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(54) Title: 13245, A NOVEL HUMAN MYOTONIC DYSTROPHY TYPE PROTEIN KINASE AND USES THEREFOR

(57) Abstract: The invention provides isolated nucleic acids molecules, designated 13245 nucleic acid molecules, which encode a novel myotonic dystrophy type protein kinase. The invention also provides antisense nucleic acid molecules, recombinant expression vectors containing 13245 nucleic acid molecules, host cells into which the expression vectors have been introduced, and non-human transgenic animals in which a 13245 gene has been introduced or disrupted. The invention still further provides isolated 13245 proteins, fusion proteins, antigenic peptides and anti-13245 antibodies. Diagnostic methods utilizing compositions of the invention are also provided.

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## TITLE OF THE INVENTION

13245, A Novel Human Myotonic Dystrophy Type Protein Kinase and  
Uses Therefor

## BACKGROUND OF THE INVENTION

Protein phosphorylation, for example at serine, threonine, and tyrosine residues, is a key regulatory mechanism for a variety of cellular processes. Protein phosphorylation is influenced primarily by enzymes of two types, namely protein kinases (PKs) and protein phosphatases (PPs). PKs catalyze addition of a phosphate moiety to a protein amino acid residue (generally a serine, threonine, or tyrosine residue), and PPs catalyze removal of such moieties. The catalytic activities of PKs and PPs are, in turn, influenced by the state of the cell and the environment in which it finds itself.

Myotonic dystrophy type PKs (MDPKs) are associated with modulation of cell morphology, shape, and contractility. MDPKs are also known to modulate the activity of skeletal muscle voltage-gated sodium channels, but not cardiac muscle voltage-gated sodium channels. MDPKs thus have a role in a variety of musculodegenerative and other musculoskeletal disorders including, for example, muscular dystrophy (MD) of various types (e.g., Duchenne's MD, limb-girdle MD, Becker MD, facioscapulohumerol MD, mitochondrial myopathy, and congenital myopathy) and myotonic dystrophies (e.g., Steinert's disease and Thomsen's disease).

Numerous MDPKs have been described, and many more are believed to exist. In view of the widespread and critical nature of MDPK activities in normal and pathological physiological processes, a need exists for identification of further members of this protein family. The present invention satisfies this need by providing a novel human MDPK.

## SUMMARY OF THE INVENTION

The present invention is based, in part, on the discovery of a novel gene encoding a MDPK, the gene being referred to herein as "13245". The nucleotide sequence of a cDNA encoding 13245 is shown in SEQ ID NO: 1, and the amino acid sequence of a 13245 polypeptide is shown in SEQ ID NO: 2. In addition, the nucleotide sequence of the coding region is depicted in SEQ ID NO: 3.

Accordingly, in one aspect, the invention features a nucleic acid molecule that encodes a 13245 protein or polypeptide, e.g., a biologically active portion of the 13245 protein. In a preferred embodiment the isolated nucleic acid molecule encodes a polypeptide having the amino acid sequence SEQ ID NO: 2. In other embodiments, the invention  
5 provides isolated 13245 nucleic acid molecules having the nucleotide sequence of either of SEQ ID NOs: 1 and 3.

In still other embodiments, the invention provides nucleic acid molecules that have sequences that are substantially identical (e.g., naturally occurring allelic variants) to the nucleotide sequence of either of SEQ ID NOs: 1 and 3. In other embodiments, the invention  
10 provides a nucleic acid molecule which hybridizes under stringent hybridization conditions with a nucleic acid molecule having a sequence comprising the nucleotide sequence of either of SEQ ID NOs: 1 and 3, wherein the nucleic acid encodes a full length 13245 protein or an active fragment thereof.

In a related aspect, the invention further provides nucleic acid constructs that  
15 include a 13245 nucleic acid molecule described herein. In certain embodiments, the nucleic acid molecules of the invention are operatively linked to native or heterologous regulatory sequences. Also included are vectors and host cells containing the 13245 nucleic acid molecules of the invention, e.g., vectors and host cells suitable for producing 13245 nucleic acid molecules and polypeptides.

20 In another related aspect, the invention provides nucleic acid fragments suitable as primers or hybridization probes for detection of 13245-encoding nucleic acids.

In still another related aspect, isolated nucleic acid molecules that are antisense to a 13245-encoding nucleic acid molecule are provided.

In another aspect, the invention features 13245 polypeptides, and biologically  
25 active or antigenic fragments thereof that are useful, e.g., as reagents or targets in assays applicable to treatment and diagnosis of 13245-mediated or related disorders (e.g., MDPK-mediated disorders such as those described herein). In another embodiment, the invention provides 13245 polypeptides having protein kinase activity. Preferred polypeptides are 13245 proteins including at least one pkinase domain, and preferably having a 13245 activity, e.g., a  
30 13245 activity as described herein. Preferred polypeptides are 13245 proteins including at least one CNH domain and at least one pkinase domain. Other preferred polypeptides are 13245 proteins including at least one CNH domain, at least one pkinase domain, at least one

phorbol ester/diacylglycerol binding domain, at least one PH domain, and at least one leucine zipper domain.

In other embodiments, the invention provides 13245 polypeptides, e.g., a 13245 polypeptide having the amino acid sequence shown in SEQ ID NO: 2,, an amino acid  
5 sequence that is substantially identical to the amino acid sequence shown in SEQ ID NO: 2; or an amino acid sequence encoded by a nucleic acid molecule having a nucleotide sequence which hybridizes under stringent hybridization conditions to a nucleic acid molecule comprising the nucleotide sequence of either of SEQ ID NOs: 1 and 3, wherein the nucleic acid encodes a full length 13245 protein or an active fragment thereof.

10 In a related aspect, the invention further provides nucleic acid constructs that include a 13245 nucleic acid molecule described herein.

In a related aspect, the invention provides 13245 polypeptides or fragments operatively linked to non-13245 polypeptides to form fusion proteins.

In another aspect, the invention features antibodies and antigen-binding  
15 fragments thereof, that react with, or more preferably, specifically bind, 13245 polypeptides.

In another aspect, the invention provides methods of screening for compounds that modulate the expression or activity of the 13245 polypeptides or nucleic acids.

In still another aspect, the invention provides a process for modulating 13245 polypeptide or nucleic acid expression or activity, e.g., using the screened compounds. In  
20 certain embodiments, the methods involve treatment of conditions related to aberrant activity or expression of the 13245 polypeptides or nucleic acids, such as conditions involving aberrant or deficient protein phosphorylation or aberrant or deficient cell process regulation (e.g., aberrant or deficient cell signaling or aberrant or deficient muscular function).

The invention also provides assays for determining the activity of or the  
25 presence or absence of 13245 polypeptides or nucleic acid molecules in a biological sample, including for disease diagnosis.

In further aspect the invention provides assays for determining the presence or absence of a genetic alteration in a 13245 polypeptide or nucleic acid molecule, including for disease diagnosis.

30 The invention also includes a method of modulating the ability of a cell to catalyze interconversion of the phosphorylated and de-phosphorylated forms a GTPase protein. The method comprises modulating 13245 protein activity in the cell. The activity of

13245 protein can be modulated by inhibiting expression of the 13245 gene in the cell, for example by administering to the cell an antisense oligonucleotide which hybridizes under stringent conditions with a transcript (e.g., an mRNA) of the 13245 gene, an antisense oligonucleotide which hybridizes under stringent conditions with a polynucleotide having the nucleotide sequence SEQ ID NO: 1, or an antisense oligonucleotide which hybridizes under stringent conditions with a polynucleotide having the nucleotide sequence SEQ ID NO: 3. Alternatively the activity of 13245 protein can be inhibited without significantly affecting 13245 gene expression in the cell. For example, the activity of 13245 protein can be inhibited by administering to the cell an agent which inhibits an activity of 13245 protein, such as an antibody which specifically binds with 13245 protein. In a related aspect, the activity of 13245 can be modulated by enhancing expression of 13245 in the cell. For example, expression of 13245 in a cell can be enhanced by administering to the cell an agent that enhances expression of 13245, such as an expression vector encoding 13245 protein.

The invention further includes a method for assessing whether a test compound is useful for modulating at least one phenomenon selected from the group consisting of (1) interconversion of the phosphorylated and de-phosphorylated forms of a serine, threonine, or tyrosine residue of a GTPase protein; (2) cell contractility; (3) cell growth; (4) cell conductivity; (5) entry of a cell into the cell cycle; (6) progression of a cell through the cell cycle; (7) mitogenesis; (8) cell metabolism; (9) gene transcription; (11) cytokinesis; (12) cell shape; (13) cell movement; (14) integration of a viral genome into a host cell genome; (15) maintenance of a viral genome within a host cell genome; (16) a cytological change in a virus-infected host cell; (17) virus production in a virus-infected host cell; (18) interaction of a virion with a membrane of a virus-infected host cell; and (19) encapsulation of a virion within a portion of a membrane of a virus-infected host cell. The method comprises:

a) adding the test compound to a first composition comprising a polypeptide that has an amino acid sequence at least 90% identical to SEQ ID NO: 2 and that exhibits a 13245 activity; and

b) comparing the 13245 activity in the first composition and in a second composition that is substantially identical to the first composition except that it does not comprise the test compound.

A difference in the 13245 activity in the first and second compositions is an indication that the test compound is useful for modulating the phenomenon.

The invention also includes another method for assessing whether a test compound is useful for modulating at least one phenomenon selected from the group consisting of (1) interconversion of the phosphorylated and de-phosphorylated forms of a serine, threonine, or tyrosine residue of a GTPase protein; (2) cell contractility; (3) cell growth; (4) cell conductivity; (5) entry of a cell into the cell cycle; (6) progression of a cell through the cell cycle; (7) mitogenesis; (8) cell metabolism; (9) gene transcription; (11) cytokinesis; (12) cell shape; (13) cell movement; (14) integration of a viral genome into a host cell genome; (15) maintenance of a viral genome within a host cell genome; (16) a cytological change in a virus-infected host cell; (17) virus production in a virus-infected host cell; (18) interaction of a virion with a membrane of a virus-infected host cell; and (19) encapsulation of a virion within a portion of a membrane of a virus-infected host cell. This method comprises:

a) adding the test compound to a first composition comprising a cell which comprises a nucleic acid that encodes a polypeptide that has an amino acid sequence at least 90% identical to SEQ ID NO: 2 and that exhibits a 13245 activity; and

b) comparing 13245 activity in the first composition and in a second composition that is substantially identical to the first composition except that it does not comprise the test compound.

A difference in the 13245 activity in the first and second compositions is an indication that the test compound is useful for modulating the phenomenon.

Compounds identified using these methods can be used to make a pharmaceutical composition for modulating the phenomenon, for example by combining it with a pharmaceutically acceptable carrier. Such compositions can be used to modulate the phenomenon in a human.

The invention includes another method for identifying a compound useful for modulating at least one phenomenon selected from the group consisting of (1) interconversion of the phosphorylated and de-phosphorylated forms of a serine, threonine, or tyrosine residue of a GTPase protein; (2) cell contractility; (3) cell growth; (4) cell conductivity; (5) entry of a cell into the cell cycle; (6) progression of a cell through the cell cycle; (7) mitogenesis; (8) cell metabolism; (9) gene transcription; (11) cytokinesis; (12) cell shape; (13) cell movement; (14) integration of a viral genome into a host cell genome; (15) maintenance of a viral genome within a host cell genome; (16) a cytological change in a virus-infected host cell; (17) virus production in a virus-infected host cell; (18) interaction of a virion with a membrane of

a virus-infected host cell; and (19) encapsulation of a virion within a portion of a membrane of a virus-infected host cell. This method comprises:

a) contacting the test compound and a polypeptide selected from the group consisting of

i) a polypeptide which is encoded by a nucleic acid molecule comprising a portion having a nucleotide sequence which is at least 90% identical to one of SEQ ID NOs: 1 and 3; and

ii) a fragment of a polypeptide having either an amino acid sequence comprising SEQ ID NO: 2, wherein the fragment comprises at least 25 contiguous amino acid residues of SEQ ID NO: 2

or a cell that expresses the polypeptide; and

b) determining whether the polypeptide binds with the test compound.

Binding of the polypeptide and the test compound is an indication that the test compound is useful for modulating the phenomenon.

Other features and advantages of the invention will be apparent from the following detailed description, and from the claims.

#### BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 depicts a cDNA sequence (SEQ ID NO: 1) and predicted amino acid sequence (SEQ ID NO: 2) of human 13245. The methionine-initiated open reading frame of human 13245 (without the 5'- and 3'-non-translated regions) starts at nucleotide 19 of SEQ ID NO: 1, and the coding region (not including the terminator codon; shown in SEQ ID NO: 3) extends through nucleotide 6178 of SEQ ID NO: 1.

Figure 2 depicts a hydropathy plot of human 13245. Relatively hydrophobic residues are shown above the dashed horizontal line, and relative hydrophilic residues are below the dashed horizontal line. The cysteine residues (cys) are indicated by short vertical lines below the hydropathy trace. The numbers corresponding to the amino acid sequence of human 13245 are indicated. Polypeptides of the invention include fragments which include: all or part of a hydrophobic sequence, i.e., a sequence above the dashed line, e.g., the sequence of about residues 195-210 of SEQ ID NO: 2; all or part of a hydrophilic sequence, i.e., a sequence below the dashed line, e.g., the sequence of residues 455-475 of SEQ ID NO: 2; a sequence which includes a cysteine residue; or a glycosylation site.

Figure 3 is an alignment of the amino acid sequence (SEQ ID NO: 2) of 13245, murine rho/rac-interacting citron kinase ("AAC72823"; GENBANK® accession no. AAC72823; SEQ ID NO: 4), murine citron-K kinase ("AAC27933"; GENBANK® accession no. AAC27933; SEQ ID NO: 5), murine citron protein ("P49025"; GENBANK® accession no. P49025; SEQ ID NO: 6), and human citron protein ("O14578"; GENBANK® accession no. O14578; SEQ ID NO: 7). The alignment was made using the Multalin v4ersion 5.4.1 software using the blosum62 symbol comparison table, a gap weight of 12, and a gap length weight of 2.

#### DETAILED DESCRIPTION

The human 13245 cDNA sequence (Figure 1; SEQ ID NO: 1), which is approximately 6575 nucleotide residues long including non-translated regions, contains a predicted methionine-initiated coding sequence of about 6160 nucleotide residues, excluding termination codon (i.e., nucleotide residues 19-6178 of SEQ ID NO: 1; also shown in SEQ ID NO: 3). The coding sequence encodes a 2053 amino acid protein having the amino acid sequence SEQ ID NO: 2.

Human 13245 contains the following regions or other structural features: a predicted pkinase domain (PF00069) at about amino acid residues 97-360 of SEQ ID NO: 2, a predicted protein kinase C terminal domain at residues 361-390 of SEQ ID NO: 2, a serine/threonine protein kinase active site signature sequence at residues 217-229 of SEQ ID NO: 2, predicted leucine zipper domains at residues 838-859, 975-996, 1041-1062, and 1143-1164 of SEQ ID NO: 2, a predicted carbamoyl-phosphate synthase sub-domain signature sequence at residues 1156-1163 of SEQ ID NO: 2, a predicted phorbol ester/diacylglycerol binding domain at residues 1389-1437 of SEQ ID NO: 2, a predicted pleckstrin homology (PH) domain at residues 1470-1525 of SEQ ID NO: 2, and a predicted CNH domain at residues 1568-1865 of SEQ ID NO: 2.

The human 13245 protein has predicted N-glycosylation sites (Pfam accession number PS00001) at about amino acid residues 819-822, 1571-1574, 1694-1697, 1717-1720, and 2026-2029 of SEQ ID NO: 2; predicted cAMP-/cGMP-dependent protein kinase phosphorylation sites (Pfam accession number PS00004) at about amino acid residues 78-81, 477-480, 579-582, 601-604, 680-683, 1322-1325, and 1366-1369 of SEQ ID NO: 2; predicted protein kinase C phosphorylation sites (Pfam accession number PS00005) at about amino acid

residues 93-95, 248-250, 308-310, 378-380, 487-489, 498-500, 516-518, 546-548, 577-579, 824-826, 872-874, 1025-1027, 1033-1035, 1096-1098, 1144-1146, 1170-1172, 1215-1217, 1268-1270, 1314-1316, 1335-1337, 1363-1365, 1376-1378, 1542-1544, 1724-1726, 1892-1894, 1910-1912, 1963-1965, and 1977-1979 of SEQ ID NO: 2; predicted casein kinase II phosphorylation sites (Pfam accession number PS00006) located at about amino acid residues 83-86, 93-96, 140-143, 361-364, 381-384, 386-389, 410-413, 436-439, 445-448, 480-483, 487-490, 501-504, 529-532, 867-870, 908-911, 935-938, 940-943, 973-976, 1015-1018, 1025-1028, 1046-4049, 1081-1084, 1142-1145, 1170-1173, 1218-1221, 1308-1311, 1314-1317, 1370-1373, 1736-1739, 1794-1797, 1864-1867, 1882-1885, 1904-1907, 1964-1967, and 2012-2015 of SEQ ID NO: 2; a predicted tyrosine kinase phosphorylation site at residues 741-747 of SEQ ID NO: 2; predicted N-myristoylation sites (Pfam accession number PS00008) at about amino acid residues 50-5, 1202-1207, 1532-1537, 1584-1589, 1675-1680, and 1999-2004 of SEQ ID NO: 2; a predicted amidation site (Pfam accession number PS00009) at about amino acid residues 134-136 of SEQ ID NO: 2.

For general information regarding PFAM identifiers, PS prefix and PF prefix domain identification numbers, refer to Sonnhammer et al. (1997, Protein 28:405-420) and <http://www.psc.edu/general/software/packages/pfam/pfam.html>.

The 13245 protein contains a significant number of structural characteristics in common with members of the MDPK family. The term "family" when referring to the protein and nucleic acid molecules of the invention means two or more proteins or nucleic acid molecules having a common structural domain or motif and having sufficient amino acid or nucleotide sequence homology as defined herein. Such family members can be naturally or non-naturally occurring and can be from either the same or different species. For example, a family can contain a first protein of human origin as well as other distinct proteins of human origin, or alternatively, can contain homologues of non-human origin, e.g., MDPK proteins for any species described in the art. Members of a family can also have common functional characteristics.

A 13245 polypeptide can include a pkinase domain. As used herein, the term "pkinase domain" refers to a protein domain having an amino acid sequence of about 200-300 amino acid residues in length, preferably, at least about 225-300 amino acids, more preferably about 264 amino acid residues and has a bit score for the alignment of the sequence to the pkinase domain (HMM) of at least 100 or greater, preferably 150 or greater, and more

preferably 200 or greater. The pkinase domain has been assigned the PFAM accession PF00069 (<http://genome.wustl.edu/Pfam/html>).

A 13245 polypeptide can include a pkinase domain. As used herein, the term "CNH domain" refers to a protein domain having an amino acid sequence of about 250-350 amino acid residues in length, preferably, at least about 275-325 amino acids, more preferably about 298 amino acid residues and has a bit score for the alignment of the sequence to the pkinase domain (HMM) of at least 100 or greater, preferably 200 or greater, and more preferably 300 or greater. The pkinase domain has been assigned the PFAM accession PF00780 (<http://genome.wustl.edu/Pfam/html>).

In a preferred embodiment, 13245 polypeptide or protein has a pkinase domain or a region which includes at least about 200-300, more preferably about 225-300, or 264 amino acid residues and has at least about 60%, 70%, 80%, 90%, 95%, 99%, or 100% homology with a pkinase domain, e.g., the pkinase domain of human 13245 (e.g., residues 97-360 of SEQ ID NO: 2).

In another preferred embodiment, 13245 polypeptide or protein has a CNH domain or a region which includes at least about 250-350, more preferably about 275-325, or 298 amino acid residues and has at least about 60%, 70%, 80%, 90%, 95%, 99%, or 100% homology with a CNH domain, e.g., the CNH domain of human 13245 (e.g., residues 1568-1865 of SEQ ID NO: 2).

To identify the presence of a pkinase or CNH domain profile in a 13245 receptor, the amino acid sequence of the protein is searched against a database of HMMs (e.g., the Pfam database, release 2.1) using the default parameters ([http://www.sanger.ac.uk/Software/Pfam/HMM\\_search](http://www.sanger.ac.uk/Software/Pfam/HMM_search)). For example, the hmmsf program, which is available as part of the HMMER package of search programs, is a family specific default program for PF00069 or PF00780 and score of 100 is the default threshold score for determining a hit. For example, using ORFAnalyzer software, a pkinase domain profile was identified in the amino acid sequence of SEQ ID NO: 2 (e.g., amino acids 53-303 of SEQ ID NO: 2). Accordingly, a 13245 protein having at least about 60-70%, more preferably about 70-80%, or about 80-90% homology with the pkinase domain profile or the CNH domain profile of human 13245 is within the scope of the invention.

While not being bound by any particular theory of operation, 13245 protein is believed to be, in at least one embodiment, a nuclear membrane protein having its carboxyl-

terminal domain oriented within the nuclear envelope. In this embodiment, 13245 protein is capable of transmitting signaling information from the cytoplasm to the nucleus, whereby, for example, gene transcription can be regulated.

In one embodiment of the invention, a 13245 polypeptide includes at least one  
5 pkinase domain. In another embodiment, the 13245 polypeptide includes at least one pkinase domain and at least one CNH domain. The 13245 molecules of the present invention can further include one or more of the N-glycosylation, cAMP-/cGMP-dependent protein kinase phosphorylation, protein kinase C phosphorylation, casein kinase II phosphorylation, tyrosine kinase phosphorylation, N-myristoylation, amidation, leucine zipper, serine/threonine protein  
10 kinase active site, carbamoyl-phosphate synthase sub-domain signature, protein kinase C terminal domain phorbol ester/diacylglycerol binding, and pleckstrin homology domains and sites described herein, and preferably comprises most or all of them.

As shown in Figure 3, 13245 protein exhibits significant sequence homology with several proteins related to citron protein, which is known to interact with GTPase  
15 enzymes of the Rho family. These GTPases include, for example, Rho-A, -B, and -C, Rac-1 and -2, and CDC42. These GTPases regulate cell structure, including cell shape, cell contraction, cell movement, distribution of structural proteins (e.g., actin) within the cell, formation of focal adhesions, cytokinesis, and cell division. These GTPases are also known to modulate gene expression in a phosphorylation-dependent manner. Proteins that are able to  
20 interact with, catalyze interconversion of phosphorylated and non-phosphorylated Rho GTPase isoforms, or both, are able to modulate these cellular processes.

Occurrence of pkinase, pkinase\_C, a protein kinase ATP-binding region signature, a serine/threonine protein kinase active site signature, a tyrosine kinase phosphorylation site, multiple potential phosphorylation sites, and similarity with citron  
25 proteins indicates that 13245 protein is able to interact with Rho GTPases and catalyze interconversion of their phosphorylated and non-phosphorylated forms. Ability of 13245 to modulate the phosphorylation state of Rho GTPases indicates that 13245 is able to modulate one or more of cell shape, cell contraction, cell movement, distribution of structural proteins (e.g., actin) within the cell, formation of focal adhesions, cytokinesis, and cell division in cells  
30 in which it is expressed. Furthermore, these characteristics indicate that 13245 protein is involved in disorders in which one or more of these processes are aberrant. 13245 molecules described herein can therefore be used to predict, diagnose, inhibit, prevent, alleviate, or cure

these disorders. Examples of disorders in which one or more of these processes are aberrant include tumorigenesis, tumor growth, tumor metastasis, and viral infection of a cell.

Expression of 13245 is greater in peripheral blood cells than in many other cell types, and enhanced expression of 13245 is observed in HIV-1-infected cells, including cells of the CCRF cell line that have been infected with this virus. HIV-1-infected cells undergo various morphological changes, and the pattern of gene expression in HIV-1-infected cells differs from the pattern observed in non-infected cells of the same type. These observations indicate that 13245 has a role in the effects of HIV-1 infection on host cells (e.g., peripheral blood mononuclear cells). Modulating 13245 expression, activity, or both in HIV-1-infected cells can modulate the processes listed above, thereby alleviating or reversing the effects of HIV-1 infection. By way of example 13245 molecules described herein can be used to inhibit insertion of the HIV-1 genome into the host cell genome, inhibit or reverse maintenance of the HIV-1 genome within the host cell genome, inhibit or reverse cytological changes induced by HIV-1 infection, inhibit HIV-1 virus production in infected cells, inhibit interaction of HIV-1 virions with the host cell cytoplasmic membrane, inhibit encapsulation of HIV-1 virus particles in portions of the host cell membrane, or inhibit HIV-1 virus release from infected cells. 13245 molecules can therefore be used to treat individuals who are infected with HIV-1 (e.g., individuals afflicted with acquired immune deficiency syndrome) or with other pathogenic viruses or to inhibit transmission of the virus from one individual to another.

Because the 13245 polypeptides of the invention can modulate 13245-mediated activities, they can be used to develop novel diagnostic and therapeutic agents for 13245-mediated or related disorders, as described below.

As used herein, a "13245 activity," "biological activity of 13245," or "functional activity of 13245," refers to an activity exerted by a 13245 protein, polypeptide or nucleic acid molecule on, for example, a 13245-responsive cell or on a 13245 substrate (e.g., a protein substrate such as a skeletal muscle voltage-gated sodium channel protein) as determined in vivo or in vitro. In one embodiment, a 13245 activity is a direct activity, such as association with a 13245 target molecule. A "target molecule" or "binding partner" of a 13245 protein is a molecule (e.g., a protein or nucleic acid) with which the 13245 protein binds or interacts in nature. In an exemplary embodiment, such a target molecule is a 13245 receptor. A 13245 activity can also be an indirect activity, such as a cellular signaling activity mediated by interaction of the 13245 protein with a 13245 receptor.

The 13245 molecules of the present invention are predicted to have similar biological activities as MDPK family members. For example, the 13245 proteins of the present invention can have one or more of the following activities:

(1) catalyzing formation of a covalent bond within or between an amino acid residue  
5 and a phosphate moiety;

(2) modulating cell contractility;

(3) modulating cell growth;

(4) modulating cell conductivity;

(5) modulating entry of a cell into the cell cycle;

10 (6) modulating progression of a cell through the cell cycle;

(7) modulating mitogenesis;

(8) modulating cell metabolism;

(9) modulating gene transcription;

(10) catalyzing interconversion of phosphorylated and non-phosphorylated forms of a  
15 GTPase, such as a Rho GTPase;

(11) modulating cytokinesis;

(12) modulating cell shape;

(13) modulating cell movement (e.g., tumor metastasis);

(14) modulating integration of a viral genome into a host cell genome;

20 (15) modulating maintenance of a viral genome within a host cell genome;

(16) modulating cytological changes in a virus-infected host cell;

(17) modulating virus production in a virus-infected host cell;

(18) modulating interaction of a virion with a membrane of a virus-infected host cell;

and

25 (19) modulating encapsulation of a virion within a portion of a membrane of a virus-infected host cell.

Thus, 13245 molecules described herein can act as novel diagnostic targets and therapeutic agents for prognosticating, diagnosing, preventing, inhibiting, alleviating, or curing MDPK-related disorders.

30 Other activities, as described below, include the ability to modulate function, survival, morphology, proliferation and/or differentiation of cells of tissues in which 13245

molecules are expressed. Thus, the 13245 molecules can act as novel diagnostic targets and therapeutic agents for controlling disorders involving aberrant activities of these cells.

The 13245 molecules can also act as novel diagnostic targets and therapeutic agents for controlling various disorders, including skeletal muscle disorders (e.g., muscular and myotonic dystrophies as described herein and in the art).

The 13245 protein, fragments thereof, and derivatives and other variants of the sequence in SEQ ID NO: 2 thereof are collectively referred to as "polypeptides or proteins of the invention" or "13245 polypeptides or proteins". Nucleic acid molecules encoding such polypeptides or proteins are collectively referred to as "nucleic acids of the invention" or "13245 nucleic acids." 13245 molecules refer to 13245 nucleic acids, polypeptides, and antibodies.

As used herein, the term "nucleic acid molecule" includes DNA molecules (e.g., a cDNA or genomic DNA) and RNA molecules (e.g., an mRNA) and analogs of the DNA or RNA generated, e.g., by the use of nucleotide analogs. The nucleic acid molecule can be single-stranded or double-stranded, but preferably is double-stranded DNA.

The term "isolated or purified nucleic acid molecule" includes nucleic acid molecules that are separated from other nucleic acid molecules that are present in the natural source of the nucleic acid. For example, with regards to genomic DNA, the term "isolated" includes nucleic acid molecules that are separated from the chromosome with which the genomic DNA is naturally associated. Preferably, an "isolated" nucleic acid is free of sequences that naturally flank the nucleic acid (i.e., sequences located at the 5'- and/or 3'-ends of the nucleic acid) in the genomic DNA of the organism from which the nucleic acid is derived. For example, in various embodiments, the isolated nucleic acid molecule can contain less than about 5 kilobases, 4 kilobases, 3 kilobases, 2 kilobases, 1 kilobase, 0.5 kilobase or 0.1 kilobase of 5'- and/or 3'-nucleotide sequences which naturally flank the nucleic acid molecule in genomic DNA of the cell from which the nucleic acid is derived. Moreover, an "isolated" nucleic acid molecule, such as a cDNA molecule, can be substantially free of other cellular material, or culture medium when produced by recombinant techniques, or substantially free of chemical precursors or other chemicals when chemically synthesized.

As used herein, the term "hybridizes under stringent conditions" describes conditions for hybridization and washing. Stringent conditions are known to those skilled in the art and can be found in available references (e.g., Current Protocols in Molecular Biology,

John Wiley & Sons, N.Y., 1989, 6.3.1-6.3.6). Aqueous and non-aqueous methods are described in that reference and either can be used. A preferred example of stringent hybridization conditions are hybridization in 6× sodium chloride/sodium citrate (SSC) at about 45°C, followed by one or more washes in 0.2× SSC, 0.1% (w/v) SDS at 50°C. Another  
5 example of stringent hybridization conditions are hybridization in 6× SSC at about 45°C, followed by one or more washes in 0.2× SSC, 0.1% (w/v) SDS at 55°C. A further example of stringent hybridization conditions are hybridization in 6× SSC at about 45°C, followed by one or more washes in 0.2× SSC, 0.1% (w/v) SDS at 60°C. Preferably, stringent hybridization conditions are hybridization in 6× SSC at about 45°C, followed by one or more washes in  
10 0.2× SSC, 0.1% (w/v) SDS at 65°C. Particularly preferred stringency conditions (and the conditions that should be used if the practitioner is uncertain about what conditions should be applied to determine if a molecule is within a hybridization limitation of the invention) are 0.5 molar sodium phosphate, 7% (w/v) SDS at 65°C, followed by one or more washes at 0.2× SSC, 1% (w/v) SDS at 65°C. Preferably, an isolated nucleic acid molecule of the invention  
15 that hybridizes under stringent conditions to the sequence of SEQ ID NO: 1 or SEQ ID NO: 3, corresponds to a naturally-occurring nucleic acid molecule.

As used herein, a "naturally-occurring" nucleic acid molecule refers to an RNA or DNA molecule having a nucleotide sequence that occurs in nature (e.g., encodes a natural protein).

20 As used herein, the terms "gene" and "recombinant gene" refer to nucleic acid molecules which include an open reading frame encoding a 13245 protein, preferably a mammalian 13245 protein, and can further include non-coding regulatory sequences and introns.

An "isolated" or "purified" polypeptide or protein is substantially free of  
25 cellular material or other contaminating proteins from the cell or tissue source from which the protein is derived, or substantially free from chemical precursors or other chemicals when chemically synthesized. In one embodiment, the language "substantially free" means preparation of 13245 protein having less than about 30%, 20%, 10% and more preferably 5% (by dry weight), of non-13245 protein (also referred to herein as a "contaminating protein"),  
30 or of chemical precursors or non-13245 chemicals. When the 13245 protein or biologically active portion thereof is recombinantly produced, it is also preferably substantially free of culture medium, i.e., culture medium represents less than about 20%, more preferably less

than about 10%, and most preferably less than about 5% of the volume of the protein preparation. The invention includes isolated or purified preparations of at least 0.01, 0.1, 1.0, and 10 milligrams in dry weight.

5 A "non-essential" amino acid residue is a residue that can be altered from the wild-type sequence of 13245 (e.g., the sequence of either of SEQ ID NOs: 1 and 3) without abolishing or, more preferably, without substantially altering a biological activity, whereas an "essential" amino acid residue results in such a change. For example, amino acid residues that are conserved among the polypeptides of the present invention, e.g., those present in the pkinase domain are predicted to be particularly non-amenable to alteration.

10 A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), non-polar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (e.g., threonine, valine, isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine). Thus, a predicted nonessential amino acid residue in a 13245 protein is preferably replaced with another amino acid residue from the same side chain family. Alternatively, in another embodiment, mutations can be introduced randomly along all or part of a 13245 coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for 13245 biological activity to identify mutants that retain activity. Following mutagenesis of SEQ ID NO: 1 or SEQ ID NO: 3, the encoded protein can be expressed recombinantly and the activity of the protein can be determined.

25 As used herein, a "biologically active portion" of a 13245 protein includes a fragment of a 13245 protein that participates in an interaction between a 13245 molecule and a non-13245 molecule. Biologically active portions of a 13245 protein include peptides comprising amino acid sequences sufficiently homologous to or derived from the amino acid sequence of the 13245 protein, e.g., the amino acid sequence shown in SEQ ID NO: 2, which include less amino acids than the full length 13245 proteins, and exhibit at least one activity of a 13245 protein. Typically, biologically active portions comprise a domain or motif with at least one activity of the 13245 protein, e.g., a domain or motif capable of catalyzing an

activity described herein, such as covalent addition of a phosphate moiety to a protein amino acid residue (e.g., to a serine or threonine hydroxyl group).

A biologically active portion of a 13245 protein can be a polypeptide that for example, 10, 25, 50, 100, 200, 300, or 400, 500, 1000, 1500, or 2000 or more amino acids in length. Biologically active portions of a 13245 protein can be used as targets for developing agents that modulate a 13245-mediated activity, e.g., a biological activity described herein.

Calculations of homology or sequence identity between sequences (the terms are used interchangeably herein) are performed as follows.

To determine the percent identity of two amino acid sequences, or of two nucleic acid sequences, the sequences are aligned for optimal comparison purposes (e.g., gaps can be introduced in one or both of a first and a second amino acid or nucleic acid sequence for optimal alignment and non-homologous sequences can be disregarded for comparison purposes). In a preferred embodiment, the length of a reference sequence aligned for comparison purposes is at least 30%, preferably at least 40%, more preferably at least 50%, even more preferably at least 60%, and even more preferably at least 70%, 80%, 90%, 100% of the length of the reference sequence (e.g., when aligning a second sequence to the 13245 amino acid sequence of SEQ ID NO: 2, 100 amino acid residues, preferably at least 200, 300, 400, 500, 1000, 1500, or 2000 or more amino acid residues are aligned). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position (as used herein amino acid or nucleic acid "identity" is equivalent to amino acid or nucleic acid "homology"). The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences.

The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. In a preferred embodiment, the percent identity between two amino acid sequences is determined using the Needleman et al. (1970, J. Mol. Biol. 48:444-453) algorithm which has been incorporated into the GAP program in the GCG software package (available at <http://www.gcg.com>), using either a BLOSUM 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or

4 and a length weight of 1, 2, 3, 4, 5, or 6. In yet another preferred embodiment, the percent identity between two nucleotide sequences is determined using the GAP program in the GCG software package (available at <http://www.gcg.com>), using a NWSgapdna.CMP matrix and a gap weight of 40, 50, 60, 70, or 80 and a length weight of 1, 2, 3, 4, 5, or 6. A particularly preferred set of parameters (and the one that should be used if the practitioner is uncertain about what parameters should be applied to determine if a molecule is within a sequence identity or homology limitation of the invention) are a BLOSUM 62 scoring matrix with a gap penalty of 12, a gap extend penalty of 4, and a frameshift gap penalty of 5.

The percent identity between two amino acid or nucleotide sequences can be determined using the algorithm of Meyers et al. (1989, CABIOS, 4:11-17) which has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4.

The nucleic acid and protein sequences described herein can be used as a "query sequence" to perform a search against public databases to, for example, identify other family members or related sequences. Such searches can be performed using the NBLAST and XBLAST programs (version 2.0) of Altschul, et al. (1990, J. Mol. Biol. 215:403-410). BLAST nucleotide searches can be performed with the NBLAST program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to 13245 nucleic acid molecules of the invention. BLAST protein searches can be performed with the XBLAST program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to 13245 protein molecules of the invention. To obtain gapped alignments for comparison purposes, gapped BLAST can be utilized as described in Altschul et al. (1997, Nucl. Acids Res. 25:3389-3402). When using BLAST and gapped BLAST programs, the default parameters of the respective programs (e.g., XBLAST and NBLAST) can be used. See <<http://www.ncbi.nlm.nih.gov>>.

"Malexpression or aberrant expression," as used herein, refers to a non-wild-type pattern of gene expression, at the RNA or protein level. It includes: expression at non-wild-type levels, i.e., over- or under-expression; a pattern of expression that differs from wild-type in terms of the time or stage at which the gene is expressed, e.g., increased or decreased expression (as compared with wild-type) at a predetermined developmental period or stage; a pattern of expression that differs from wild-type in terms of decreased expression (as compared with wild-type) in a predetermined cell type or tissue type; a pattern of expression that differs from wild-type in terms of the splicing size, amino acid sequence, post-translational

modification, or biological activity of the expressed polypeptide; a pattern of expression that differs from wild-type in terms of the effect of an environmental stimulus or extracellular stimulus on expression of the gene, e.g., a pattern of increased or decreased expression (as compared with wild-type) in the presence of an increase or decrease in the strength of the stimulus.

"Subject," as used herein, can refer to a mammal, e.g., a human, or to an experimental or animal or disease model. The subject can also be a non-human animal, e.g., a horse, cow, goat, or other domestic animal.

A "purified preparation of cells," as used herein, refers to, in the case of plant or animal cells, an in vitro preparation of cells and not an entire intact plant or animal. In the case of cultured cells or microbial cells, it consists of a preparation of at least 10%, and more preferably, 50% of the subject cells.

Various aspects of the invention are described in further detail below.

#### Isolated Nucleic Acid Molecules

In one aspect, the invention provides, an isolated or purified, nucleic acid molecule that encodes a 13245 polypeptide described herein, e.g., a full-length 13245 protein or a fragment thereof, e.g., a biologically active portion of 13245 protein. Also included is a nucleic acid fragment suitable for use as a hybridization probe, which can be used, e.g., to identify nucleic acid molecule encoding a polypeptide of the invention, 13245 mRNA, and fragments suitable for use as primers, e.g., PCR primers for the amplification or mutation of nucleic acid molecules.

In one embodiment, an isolated nucleic acid molecule of the invention includes the nucleotide sequence shown in SEQ ID NO: 1 or a portion thereof. In one embodiment, the nucleic acid molecule includes sequences encoding the human 13245 protein (i.e., "the coding region," from nucleotides 19-6178 of SEQ ID NO: 1), as well as 5'-non-translated sequences (nucleotides 1-18 of SEQ ID NO: 1) or 3'-non-translated sequences (nucleotides 6179-6575 of SEQ ID NO: 1). Alternatively, the nucleic acid molecule can include only the coding region of SEQ ID NO: 1 (e.g., nucleotides 19-6178, corresponding to SEQ ID NO: 3) and, e.g., no flanking sequences which normally accompany the subject sequence. In another embodiment, the nucleic acid molecule encodes a sequence corresponding to the 2053 amino acid residue protein of SEQ ID NO: 2.

In another embodiment, an isolated nucleic acid molecule of the invention includes a nucleic acid molecule which is a complement of the nucleotide sequence shown in one of SEQ ID NOs: 1 and 3, and a portion of either of these sequences. In other embodiments, the nucleic acid molecule of the invention is sufficiently complementary to the nucleotide sequence shown in either of SEQ ID NOs: 1 and 3 that it can hybridize with a nucleic acid having that sequence, thereby forming a stable duplex.

In one embodiment, an isolated nucleic acid molecule of the invention includes a nucleotide sequence which is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% or more homologous to the entire length of the nucleotide sequence shown in one of SEQ ID NO: 1, SEQ ID NO: 3, and a portion, preferably of the same length, of either of these nucleotide sequences.

#### 13245 Nucleic Acid Fragments

A nucleic acid molecule of the invention can include only a portion of the nucleic acid sequence of either of SEQ ID NOs: 1 and 3. For example, such a nucleic acid molecule can include a fragment that can be used as a probe or primer or a fragment encoding a portion of a 13245 protein, e.g., an immunogenic or biologically active portion of a 13245 protein. A fragment can comprise nucleotides corresponding to residues 97-360 of SEQ ID NO: 2, which encodes a pkinase domain of human 13245, or to residues 1568-1865 of SEQ ID NO: 2, which encodes a CNH domain of human 13245. The nucleotide sequence determined from the cloning of the 13245 gene facilitates generation of probes and primers for use in identifying and/or cloning other 13245 family members, or fragments thereof, as well as 13245 homologues, or fragments thereof, from other species.

In another embodiment, a nucleic acid includes a nucleotide sequence that includes part, or all, of the coding region and extends into either (or both) the 5'- or 3'-non-coding region. Other embodiments include a fragment that includes a nucleotide sequence encoding an amino acid fragment described herein. Nucleic acid fragments can encode a specific domain or site described herein or fragments thereof, particularly fragments thereof that are at least about 250 amino acids in length. Fragments also include nucleic acid sequences corresponding to specific amino acid sequences described above or fragments thereof. Nucleic acid fragments should not to be construed as encompassing those fragments that may have been disclosed prior to the invention.

A nucleic acid fragment can include a sequence corresponding to a domain, region, or functional site described herein. A nucleic acid fragment can also include one or more domain, region, or functional site described herein.

13245 probes and primers are provided. Typically a probe/primer is an isolated or purified oligonucleotide. The oligonucleotide typically includes a region of nucleotide sequence that hybridizes under stringent conditions to at least about 7, 12 or 15, preferably about 20 or 25, more preferably about 30, 35, 40, 45, 50, 55, 60, 65, or 75 consecutive nucleotides of a sense or antisense sequence of either of SEQ ID NOs: 1 and 3, and a naturally occurring allelic variant or mutant of either of SEQ ID NOs: 1 and 3.

In a preferred embodiment the nucleic acid is a probe which is at least 5 or 10, and less than 200, more preferably less than 100, or less than 50, base pairs in length. It should be identical, or differ by 1, or fewer than 5 or 10 bases, from a sequence disclosed herein. If alignment is needed for this comparison the sequences should be aligned for maximum homology. "Looped" out sequences from deletions or insertions, or mismatches, are considered differences.

A probe or primer can be derived from the sense or anti-sense strand of a nucleic acid that encodes a pkinase domain at about amino acid residues 97 to 360 of SEQ ID NO: 2 or the predicted CNH domain at about amino acid residues 1568 to 1865 of SEQ ID NO: 2.

In another embodiment a set of primers is provided, e.g., primers suitable for use in a PCR, which can be used to amplify a selected region of a 13245 sequence. The primers should be at least 5, 10, or 50 base pairs in length and less than 100, or less than 200, base pairs in length. The primers should be identical, or differs by one base from a sequence disclosed herein or from a naturally occurring variant. Primers suitable for amplifying all or a portion of any of the following regions are provided: e.g., one or more a pkinase domain and the predicted CNH domain, as defined above relative to SEQ ID NO: 2.

A nucleic acid fragment can encode an epitope bearing region of a polypeptide described herein.

A nucleic acid fragment encoding a "biologically active portion of a 13245 polypeptide" can be prepared by isolating a portion of the nucleotide sequence of either of SEQ ID NOs: 1 and 3, which encodes a polypeptide having a 13245 biological activity (e.g., the biological activities of the 13245 proteins are described herein), expressing the encoded

portion of the 13245 protein (e.g., by recombinant expression in vitro) and assessing the activity of the encoded portion of the 13245 protein. For example, a nucleic acid fragment encoding a biologically active portion of 13245 includes a pkinase domain, e.g., amino acid residues 97 to 360 of SEQ ID NO: 2, or a CNH domain, e.g., amino acid residues 1568 to 1865 of SEQ ID NO: 2. A nucleic acid fragment encoding a biologically active portion of a 13245 polypeptide can comprise a nucleotide sequence that is greater than 25 or more nucleotides in length.

In one embodiment, a nucleic acid includes one that has a nucleotide sequence which is greater than 260, 300, 400, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500, 2000, 2500, 3000, 4000, 5000, or 6000 or more nucleotides in length and that hybridizes under stringent hybridization conditions with a nucleic acid molecule having the sequence of either of SEQ ID NOs: 1 and 3.

#### 13245 Nucleic Acid Variants

The invention further encompasses nucleic acid molecules having a sequence that differs from the nucleotide sequence shown in either of SEQ ID NOs: 1 and 3. Such differences can be attributable to degeneracy of the genetic code (i.e., differences which result in a nucleic acid that encodes the same 13245 proteins as those encoded by the nucleotide sequence disclosed herein). In another embodiment, an isolated nucleic acid molecule of the invention encodes a protein having an amino acid sequence which differs by at least 1, but by fewer than 5, 10, 20, 50, or 100, amino acid residues from SEQ ID NO: 2. If alignment is needed for this comparison the sequences should be aligned for maximum homology. "Looped" out sequences from deletions or insertions, or mismatches, are considered differences.

Nucleic acids of the invention can be chosen for having codons, which are preferred, or non-preferred, for a particular expression system. For example, the nucleic acid can be one in which at least one codon, at preferably at least 10%, or 20% of the codons has been altered such that the sequence is optimized for expression in E. coli, yeast, human, insect, or CHO cells.

Nucleic acid variants can be naturally occurring, such as allelic variants (same locus), homologs (different locus), and orthologs (different organism) or can be non-naturally occurring. Non-naturally occurring variants can be made by mutagenesis techniques,

including those applied to polynucleotides, cells, or organisms. The variants can contain nucleotide substitutions, deletions, inversions and insertions. Variation can occur in either or both the coding and non-coding regions. The variations can produce both conservative and non-conservative amino acid substitutions (as compared in the encoded product).

5 In a preferred embodiment, the nucleic acid has a sequence that differs from that of either of SEQ ID NOs: 1 and 3, e.g., as follows: by at least one, but by fewer than 10, 20, 30, or 40, nucleotide residues; or by at least one but by fewer than 1%, 5%, 10% or 20% of the nucleotide residues in the subject nucleic acid. If necessary for this analysis the sequences should be aligned for maximum homology. "Looped" out sequences from  
10 deletions or insertions, or mismatches, are considered differences.

Orthologs, homologs, and allelic variants can be identified using methods known in the art. These variants comprise a nucleotide sequence encoding a polypeptide that is 50%, at least about 55%, typically at least about 70-75%, more typically at least about 80-85%, and most typically at least about 90-95% or more identical to the nucleotide sequence  
15 shown in either of SEQ ID NOs: 1 and 3, or a fragment of one of these sequences. Such nucleic acid molecules can readily be identified as being able to hybridize under stringent conditions, to the nucleotide sequence shown in either of SEQ ID NOs: 1 and 3, or a fragment of one of these sequences. Nucleic acid molecules corresponding to orthologs, homologs, and allelic variants of the 13245 cDNAs of the invention can further be isolated by mapping to the  
20 same chromosome or locus as the 13245 gene.

Preferred variants include those that are correlated with any of the 13245 biological activities described herein, e.g., catalyzing formation of a covalent bond between an amino acid residue of a protein (e.g., a serine or threonine residue) and a phosphate moiety.

Allelic variants of 13245 (e.g., human 13245) include both functional and non-  
25 functional proteins. Functional allelic variants are naturally occurring amino acid sequence variants of the 13245 protein within a population that maintain the ability to mediate any of the 13245 biological activities described herein.

Functional allelic variants will typically contain only conservative substitution of one or more amino acids of SEQ ID NO: 2, or substitution, deletion or insertion of non-  
30 critical residues in non-critical regions of the protein. Non-functional allelic variants are naturally-occurring amino acid sequence variants of the 13245 (e.g., human 13245) protein within a population that do not have the ability to mediate any of the 13245 biological

activities described herein. Non-functional allelic variants will typically contain a non-conservative substitution, a deletion, or insertion, or premature truncation of the amino acid sequence of SEQ ID NO: 2, or a substitution, insertion, or deletion in critical residues or critical regions of the protein.

5                   Moreover, nucleic acid molecules encoding other 13245 family members and, thus, which have a nucleotide sequence which differs from the 13245 sequences of either of SEQ ID NOs: 1 and 3 are within the scope of the invention.

#### 10                   Antisense Nucleic Acid Molecules, Ribozymes and Modified 13245 Nucleic Acid Molecules

In another aspect, the invention features, an isolated nucleic acid molecule that is antisense to 13245. An "antisense" nucleic acid can include a nucleotide sequence that is complementary to a "sense" nucleic acid encoding a protein, e.g., complementary to the coding strand of a double-stranded cDNA molecule or complementary to an mRNA sequence.

15   The antisense nucleic acid can be complementary to an entire 13245 coding strand, or to only a portion thereof (e.g., the coding region of human 13245 corresponding to SEQ ID NO: 3). In another embodiment, the antisense nucleic acid molecule is antisense to a "non-coding region" of the coding strand of a nucleotide sequence encoding 13245 (e.g., the 5'- and 3'-non-translated regions).

20                   An antisense nucleic acid can be designed such that it is complementary to the entire coding region of 13245 mRNA, but more preferably is an oligonucleotide that is antisense to only a portion of the coding or non-coding region of 13245 mRNA. For example, the antisense oligonucleotide can be complementary to the region surrounding the translation start site of 13245 mRNA, e.g., between the -10 and +10 regions of the target gene nucleotide

25   sequence of interest. An antisense oligonucleotide can be, for example, about 7, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, or 80 or more nucleotide residues in length.

An antisense nucleic acid of the invention can be constructed using chemical synthesis and enzymatic ligation reactions using procedures known in the art. For example, an antisense nucleic acid (e.g., an antisense oligonucleotide) can be chemically synthesized

30   using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the antisense and sense nucleic acids, e.g., phosphorothioate derivatives and

acridine substituted nucleotides can be used. The antisense nucleic acid also can be produced biologically using an expression vector into which a nucleic acid has been sub-cloned in an antisense orientation (i.e., RNA transcribed from the inserted nucleic acid will be of an antisense orientation to a target nucleic acid of interest, described further in the following subsection).

The antisense nucleic acid molecules of the invention are typically administered to a subject (e.g., by direct injection at a tissue site), or generated in situ such that they hybridize with or bind to cellular mRNA and/or genomic DNA encoding a 13245 protein to thereby inhibit expression of the protein, e.g., by inhibiting transcription and/or translation. Alternatively, antisense nucleic acid molecules can be modified to target selected cells and then administered systemically. For systemic administration, antisense molecules can be modified such that they specifically bind to receptors or antigens expressed on a selected cell surface, e.g., by linking the antisense nucleic acid molecules to peptides or antibodies that bind to cell surface receptors or antigens. The antisense nucleic acid molecules can also be delivered to cells using the vectors described herein. To achieve sufficient intracellular concentrations of the antisense molecules, vector constructs in which the antisense nucleic acid molecule is placed under the control of a strong pol II or pol III promoter are preferred.

In yet another embodiment, the antisense nucleic acid molecule of the invention is an alpha-anomeric nucleic acid molecule. An alpha-anomeric nucleic acid molecule forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual beta-units, the strands run parallel to each other (Gaultier et al., 1987, Nucl. Acids. Res. 15:6625-6641). The antisense nucleic acid molecule can also comprise a 2'-o-methylribonucleotide (Inoue et al., 1987, Nucl. Acids Res. 15:6131-6148) or a chimeric RNA-DNA analogue (Inoue et al., 1987, FEBS Lett. 215:327-330).

In still another embodiment, an antisense nucleic acid of the invention is a ribozyme. A ribozyme having specificity for a 13245-encoding nucleic acid can include one or more sequences complementary to the nucleotide sequence of a 13245 cDNA disclosed herein (i.e., SEQ ID NO: 1 or SEQ ID NO: 3), and a sequence having known catalytic sequence responsible for mRNA cleavage (see, for example, U.S. Patent number 5,093,246 or Haselhoff et al. (1988, Nature 334:585-591). For example, a derivative of a Tetrahymena L-19 IVS RNA can be constructed in which the nucleotide sequence of the active site is

complementary to the nucleotide sequence to be cleaved in a 13245-encoding mRNA (e.g., U.S. Patent number 4,987,071; and U.S. Patent number 5,116,742). Alternatively, 13245 mRNA can be used to select a catalytic RNA having a specific ribonuclease activity from a pool of RNA molecules (e.g., Bartel et al., 1993, Science 261:1411-1418).

5           13245 gene expression can be inhibited by targeting nucleotide sequences complementary to the regulatory region of the 13245 (e.g., the 13245 promoter and/or enhancers) to form triple helical structures that prevent transcription of the 13245 gene in target cells (Helene, 1991, Anticancer Drug Des. 6:569-584; Helene, et al., 1992, Ann. N.Y. Acad. Sci. 660:27-36; Maher, 1992, Bioassays 14:807-815). The potential sequences that can  
10 be targeted for triple helix formation can be increased by creating a so-called "switchback" nucleic acid molecule. Switchback molecules are synthesized in an alternating 5' to 3', 3' to 5' manner, such that they hybridize with first one strand of a duplex and then the other, eliminating the necessity for a sizeable stretch of either purines or pyrimidines to be present on one strand of a duplex.

15           The invention also provides detectably labeled oligonucleotide primer and probe molecules. Typically, such labels are chemiluminescent, fluorescent, radioactive, or colorimetric.

          A 13245 nucleic acid molecule can be modified at the base moiety, sugar moiety or phosphate backbone to improve, e.g., the stability, hybridization, or solubility of the  
20 molecule. For example, the deoxyribose phosphate backbone of the nucleic acid molecules can be modified to generate peptide nucleic acids (Hyrup et al., 1996, Bioorg. Med. Chem. 4:5-23). As used herein, the terms "peptide nucleic acid" (PNA) refers to a nucleic acid mimic, e.g., a DNA mimic, in which the deoxyribose phosphate backbone is replaced by a pseudopeptide backbone and only the four natural nucleobases are retained. The neutral  
25 backbone of a PNA can allow for specific hybridization to DNA and RNA under conditions of low ionic strength. The synthesis of PNA oligomers can be performed using standard solid phase peptide synthesis protocols as described in Hyrup et al. (1996, supra; Perry-O'Keefe et al., Proc. Natl. Acad. Sci. USA 93:14670-14675).

          PNAs of 13245 nucleic acid molecules can be used in therapeutic and  
30 diagnostic applications. For example, PNAs can be used as antisense or anti-gene agents for sequence-specific modulation of gene expression by, for example, inducing transcription or translation arrest or inhibiting replication. PNAs of 13245 nucleic acid molecules can also be

used in the analysis of single base pair mutations in a gene, (e.g., by PNA-directed PCR clamping); as 'artificial restriction enzymes' when used in combination with other enzymes, (e.g., S1 nucleases, as described in Hyrup et al., 1996, supra); or as probes or primers for DNA sequencing or hybridization (Hyrup et al., 1996, supra; Perry-O'Keefe, supra).

5           In other embodiments, the oligonucleotide can include other appended groups such as peptides (e.g., for targeting host cell receptors in vivo), or agents facilitating transport across the cell membrane (e.g., Letsinger et al., 1989, Proc. Natl. Acad. Sci. USA 86:6553-6556; Lemaitre et al., 1987, Proc. Natl. Acad. Sci. USA 84:648-652; PCT publication number WO 88/09810) or the blood-brain barrier (see, e.g., PCT publication number WO 89/10134).

10       In addition, oligonucleotides can be modified with hybridization-triggered cleavage agents (e.g., Krol et al., 1988, Bio-Techniques 6:958-976) or intercalating agents (e.g., Zon, 1988, Pharm. Res. 5:539-549). To this end, the oligonucleotide can be conjugated to another molecule, (e.g., a peptide, hybridization triggered cross-linking agent, transport agent, or hybridization-triggered cleavage agent).

15           The invention also includes molecular beacon oligonucleotide primer and probe molecules having at least one region which is complementary to a 13245 nucleic acid of the invention, two complementary regions, one having a fluorophore and the other having a quencher, such that the molecular beacon is useful for quantitating the presence of the 13245 nucleic acid of the invention in a sample. Molecular beacon nucleic acids are described, for

20       example, in U.S. Patent number. 5,854,033, U.S. Patent number 5,866,336, and U.S. Patent number 5,876,930.

#### Isolated 13245 Polypeptides

          In another aspect, the invention features, an isolated 13245 protein, or

25       fragment, e.g., a biologically active portion, for use as immunogens or antigens to raise or test (or more generally to bind) anti-13245 antibodies. 13245 protein can be isolated from cells or tissue sources using standard protein purification techniques. 13245 protein or fragments thereof can be produced by recombinant DNA techniques or synthesized chemically.

          Polypeptides of the invention include those that arise as a result of the

30       existence of multiple genes, alternative transcription events, alternative RNA splicing events, and alternative translational and post-translational events. The polypeptide can be expressed in systems, e.g., cultured cells, which result in substantially the same post-translational

modifications present when the polypeptide is expressed in a native cell, or in systems which result in the alteration or omission of post-translational modifications, e.g., glycosylation or cleavage, present when expressed in a native cell.

In a preferred embodiment, a 13245 polypeptide has one or more of the  
5 following characteristics:

(1) it catalyzes formation of a covalent bond within or between an amino acid residue and a phosphate moiety;

(2) it modulates cell contractility;

(3) it modulates cell growth;

10 (4) it modulates cell conductivity;

(5) it modulates entry of a cell into the cell cycle;

(6) it modulates progression of a cell through the cell cycle;

(7) it modulates mitogenesis;

(8) it modulates cell metabolism; and

15 (9) it modulates gene transcription;

(10) it catalyzes interconversion of phosphorylated and non-phosphorylated forms of  
a GTPase, such as a Rho GTPase;

(11) it modulates cytokinesis;

(12) it modulates cell shape;

20 (13) it modulates cell movement (e.g., tumor metastasis);

(14) it modulates integration of a viral genome into a host cell genome;

(15) it modulates maintenance of a viral genome within a host cell genome;

(16) it modulates cytological changes in a virus-infected host cell;

(17) it modulates virus production in a virus-infected host cell;

25 (18) it modulates interaction of a virion with a membrane of a virus-infected host cell;

(19) it modulates encapsulation of a virion within a portion of a membrane of a virus-  
infected host cell

(20) it has a molecular weight, amino acid composition or other physical  
characteristic of a 13245 protein of SEQ ID NO: 2;

30 (21) it has an overall sequence similarity (identity) of at least 60-65%, preferably at  
least 70%, more preferably at least 75, 80, 85, 86, 87, 88, 89, 90, 91, 92, 93,  
94, 95, 96, 97, 98, or 99% or more, with a portion of SEQ ID NO: 2;

(22) it has a CNH domain which is preferably about 70%, 80%, 90%, 95%, 96%, 97%, 98%, or 99% or more, identical with amino acid residues 1568-1865 of SEQ ID NO: 2; or

(23) it has at least one pkinase domain which is preferably about 70%, 80%, 90%, 95%, 96%, 97%, 98%, or 99% or more, identical with amino acid residues 97-360 of SEQ ID NO: 2.

In a preferred embodiment, the 13245 protein or fragment thereof differs only insubstantially, if at all, from the corresponding sequence in SEQ ID NO: 2. In one embodiment, it differs by at least one, but by fewer than 15, 10 or 5 amino acid residues. In another, it differs from the corresponding sequence in SEQ ID NO: 2 by at least one residue but fewer than 20%, 15%, 10% or 5% of the residues differ from the corresponding sequence in SEQ ID NO: 2 (if this comparison requires alignment the sequences should be aligned for maximum homology. "Looped" out sequences from deletions or insertions, or mismatches, are considered differences). The differences are, preferably, differences or changes at a non-essential amino acid residues or involve a conservative substitution of one residue for another. In a preferred embodiment the differences are not in residues 97-360 or 1568-1865 of SEQ ID NO: 2.

Other embodiments include a protein that has one or more changes in amino acid sequence, relative to SEQ ID NO: 2 (e.g., a change in an amino acid residue which is not essential for activity). Such 13245 proteins differ in amino acid sequence from SEQ ID NO: 2, yet retain biological activity.

In one embodiment, the protein includes an amino acid sequence at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98% or more homologous to SEQ ID NO: 2.

A 13245 protein or fragment is provided which has an amino acid sequence which varies from SEQ ID NO: 2 in one or both of the regions corresponding to residues 1-96, 361-1567, and 1866-2053 of SEQ ID NO: 2 by at least one, but by fewer than 15, 10 or 5 amino acid residues, but which does not differ from SEQ ID NO: 2 in the region corresponding to residues 97-360 and 1568-1865 of SEQ ID NO: 2 (if this comparison requires alignment the sequences should be aligned for maximum homology. "Looped" out sequences from deletions or insertions, or mismatches, are considered differences). In some embodiments the difference is at a non-essential residue or is a conservative substitution, while in others the difference is at an essential residue or is a non-conservative substitution.

A biologically active portion of a 13245 protein should include the 13245 pkinase domain, the 13245 CNH domain, or both. Moreover, other biologically active portions, in which other regions of the protein are deleted, can be prepared by recombinant techniques and evaluated for one or more of the functional activities of a native 13245 protein.

In a preferred embodiment, the 13245 protein has the amino acid sequence SEQ ID NO: 2. In other embodiments, the 13245 protein is substantially identical to SEQ ID NO: 2. In yet another embodiment, the 13245 protein is substantially identical to SEQ ID NO: 2 and retains the functional activity of the protein of SEQ ID NO: 2.

#### 13245 Chimeric or Fusion Proteins

In another aspect, the invention provides 13245 chimeric or fusion proteins. As used herein, a 13245 "chimeric protein" or "fusion protein" includes a 13245 polypeptide linked to a non-13245 polypeptide. A "non-13245 polypeptide" refers to a polypeptide having an amino acid sequence corresponding to a protein which is not substantially homologous to the 13245 protein, e.g., a protein which is different from the 13245 protein and which is derived from the same or a different organism. The 13245 polypeptide of the fusion protein can correspond to all or a portion e.g., a fragment described herein of a 13245 amino acid sequence. In a preferred embodiment, a 13245 fusion protein includes at least one or more biologically active portions of a 13245 protein. The non-13245 polypeptide can be fused to the amino or carboxyl terminus of the 13245 polypeptide.

The fusion protein can include a moiety that has a high affinity for a ligand. For example, the fusion protein can be a GST-13245 fusion protein in which the 13245 sequences are fused to the carboxyl terminus of the GST sequences. Such fusion proteins can facilitate the purification of recombinant 13245. Alternatively, the fusion protein can be a 13245 protein containing a heterologous signal sequence at its amino terminus. In certain host cells (e.g., mammalian host cells), expression and/or secretion of 13245 can be increased through use of a heterologous signal sequence.

Fusion proteins can include all or a part of a serum protein, e.g., an IgG constant region, or human serum albumin.

The 13245 fusion proteins of the invention can be incorporated into pharmaceutical compositions and administered to a subject in vivo. The 13245 fusion

proteins can be used to affect the bioavailability of a 13245 substrate. 13245 fusion proteins can be useful therapeutically for the treatment of disorders caused by, for example, (i) aberrant modification or mutation of a gene encoding a 13245 protein; (ii) mis-regulation of the 13245 gene; and (iii) aberrant post-translational modification of a 13245 protein.

5 Moreover, the 13245-fusion proteins of the invention can be used as immunogens to produce anti-13245 antibodies in a subject, to purify 13245 ligands and in screening assays to identify molecules that inhibit the interaction of 13245 with a 13245 substrate.

Expression vectors are commercially available that already encode a fusion  
10 moiety (e.g., a GST polypeptide). A 13245-encoding nucleic acid can be cloned into such an expression vector such that the fusion moiety is linked in-frame to the 13245 protein.

#### Variants of 13245 Proteins

In another aspect, the invention also features a variant of a 13245 polypeptide,  
15 e.g., which functions as an agonist (mimetics) or as an antagonist. Variants of the 13245 proteins can be generated by mutagenesis, e.g., discrete point mutation, the insertion or deletion of sequences or the truncation of a 13245 protein. An agonist of the 13245 proteins can retain substantially the same, or a subset, of the biological activities of the naturally occurring form of a 13245 protein. An antagonist of a 13245 protein can inhibit one or more  
20 of the activities of the naturally occurring form of the 13245 protein by, for example, competitively modulating a 13245-mediated activity of a 13245 protein. Thus, specific biological effects can be elicited by treatment with a variant of limited function. Preferably, treatment of a subject with a variant having a subset of the biological activities of the naturally occurring form of the protein has fewer side effects in a subject relative to treatment  
25 with the naturally occurring form of the 13245 protein.

Variants of a 13245 protein can be identified by screening combinatorial libraries of mutants, e.g., truncation mutants, of a 13245 protein for agonist or antagonist activity.

Libraries of fragments e.g., amino-terminal, carboxyl-terminal, or internal  
30 fragments, of a 13245 protein coding sequence can be used to generate a variegated population of fragments for screening and subsequent selection of variants of a 13245 protein.

Variants in which a cysteine residue is added or deleted or in which a residue that is glycosylated is added or deleted are particularly preferred.

Methods for screening gene products of combinatorial libraries made by point mutations or truncation, and for screening cDNA libraries for gene products having a selected  
5 property. Recursive ensemble mutagenesis (REM), a technique which enhances the frequency of functional mutants in the libraries, can be used in combination with the screening assays to identify 13245 variants (Arkin et al., 1992, Proc. Natl. Acad. Sci. USA 89:7811-7815; Delgrave et al., 1993, Protein Engr. 6:327-331).

Cell based assays can be exploited to analyze a variegated 13245 library. For  
10 example, a library of expression vectors can be transfected into a cell line, e.g., a cell line, which ordinarily responds to 13245 in a substrate-dependent manner. The transfected cells are then contacted with 13245 and the effect of the expression of the mutant on signaling by the 13245 substrate can be detected, e.g., by measuring changes in cell growth and/or enzymatic activity. Plasmid DNA can then be recovered from the cells that score for  
15 inhibition, or alternatively, potentiation of signaling by the 13245 substrate, and the individual clones further characterized.

In another aspect, the invention features a method of making a 13245 polypeptide, e.g., a peptide having a non-wild-type activity, e.g., an antagonist, agonist, or super agonist of a naturally-occurring 13245 polypeptide, e.g., a naturally-occurring 13245  
20 polypeptide. The method includes: altering the sequence of a 13245 polypeptide, e.g., altering the sequence, e.g., by substitution or deletion of one or more residues of a non-conserved region, a domain or residue disclosed herein, and testing the altered polypeptide for the desired activity.

In another aspect, the invention features a method of making a fragment or  
25 analog of a 13245 polypeptide a biological activity of a naturally occurring 13245 polypeptide. The method includes: altering the sequence, e.g., by substitution or deletion of one or more residues, of a 13245 polypeptide, e.g., altering the sequence of a non-conserved region, or a domain or residue described herein, and testing the altered polypeptide for the desired activity.

### Anti-13245 Antibodies

In another aspect, the invention provides an anti-13245 antibody. The term "antibody" as used herein refers to an immunoglobulin molecule or immunologically active portion thereof, i.e., an antigen-binding portion. Examples of immunologically active portions of immunoglobulin molecules include F(ab) and F(ab')<sub>2</sub> fragments which can be generated by treating the antibody with an enzyme such as pepsin.

The antibody can be a polyclonal, monoclonal, recombinant, e.g., a chimeric or humanized, fully-human, non-human, e.g., murine, or single chain antibody. In a preferred embodiment, it has effector function and can fix complement. The antibody can be coupled to a toxin or imaging agent.

A full-length 13245 protein or, antigenic peptide fragment of 13245 can be used as an immunogen or can be used to identify anti-13245 antibodies made with other immunogens, e.g., cells, membrane preparations, and the like. The antigenic peptide of 13245 should include at least 8 amino acid residues of the amino acid sequence shown in SEQ ID NO: 2 and encompasses an epitope of 13245. Preferably, the antigenic peptide includes at least 10 amino acid residues, more preferably at least 15 amino acid residues, even more preferably at least 20 amino acid residues, and most preferably at least 30 amino acid residues.

Fragments of 13245 which include about residues 195-210 of SEQ ID NO: 2 can be used to make antibodies, e.g., for use as immunogens or to characterize the specificity of an antibody, against hydrophobic regions of the 13245 protein. Similarly, a fragment of 13245 which include about residues 455-475 of SEQ ID NO: 2 can be used to make an antibody against a hydrophilic region of the 13245 protein.

Antibodies reactive with, or specific for, any of these regions, or other regions or domains described herein are provided.

Preferred epitopes encompassed by the antigenic peptide are regions of 13245 are located on the surface of the protein, e.g., hydrophilic regions, as well as regions with high antigenicity. For example, an Emini surface probability analysis of the human 13245 protein sequence can be used to indicate the regions that have a particularly high probability of being localized to the surface of the 13245 protein and are thus likely to constitute surface residues useful for targeting antibody production.

In a preferred embodiment the antibody binds an epitope on any domain or region on 13245 proteins described herein.

Chimeric, humanized, but most preferably, completely human antibodies are desirable for applications which include repeated administration, e.g., therapeutic treatment  
5 (and some diagnostic applications) of human patients.

The anti-13245 antibody can be a single chain antibody. A single-chain antibody (scFV) can be engineered (e.g., Colcher et al., 1999, Ann. N.Y. Acad. Sci. 880:263-280; Reiter, 1996, Clin. Cancer Res. 2:245-252). The single chain antibody can be dimerized or multimerized to generate multivalent antibodies having specificities for different epitopes  
10 of the same target 13245 protein.

In a preferred embodiment, the antibody has reduced or no ability to bind an Fc receptor. For example, it can be an isotype, subtype, fragment or other mutant, which does not support binding to an Fc receptor, e.g., it can have a mutated or deleted Fc receptor binding region.

15 An anti-13245 antibody (e.g., monoclonal antibody) can be used to isolate 13245 by standard techniques, such as affinity chromatography or immunoprecipitation. Moreover, an anti-13245 antibody can be used to detect 13245 protein (e.g., in a cellular lysate or cell supernatant) in order to evaluate the abundance and pattern of expression of the protein. Anti-13245 antibodies can be used diagnostically to monitor protein levels in tissue  
20 as part of a clinical testing procedure, e.g., to, for example, determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling (i.e., physically linking) the antibody to a detectable substance (i.e., antibody labeling). Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes  
25 include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes  
30 luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin, and examples of suitable radioactive material include  $^{125}\text{I}$ ,  $^{131}\text{I}$ ,  $^{35}\text{S}$  or  $^3\text{H}$ .

### Recombinant Expression Vectors, Host Cells and Genetically Engineered Cells

In another aspect, the invention includes, vectors, preferably expression vectors, containing a nucleic acid encoding a polypeptide described herein. As used herein, the term "vector" refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked and can include a plasmid, cosmid or viral vector. The vector  
5 can be capable of autonomous replication or it can integrate into a host DNA. Viral vectors include, e.g., replication defective retroviruses, adenoviruses and adeno-associated viruses.

A vector can include a 13245 nucleic acid in a form suitable for expression of the nucleic acid in a host cell. Preferably the recombinant expression vector includes one or  
10 more regulatory sequences operatively linked to the nucleic acid sequence to be expressed. The term "regulatory sequence" includes promoters, enhancers and other expression control elements (e.g., polyadenylation signals). Regulatory sequences include those that direct constitutive expression of a nucleotide sequence, as well as tissue-specific regulatory and/or inducible sequences. The design of the expression vector can depend on such factors as the  
15 choice of the host cell to be transformed, the level of expression of protein desired, and the like. The expression vectors of the invention can be introduced into host cells to thereby produce proteins or polypeptides, including fusion proteins or polypeptides, encoded by nucleic acids as described herein (e.g., 13245 proteins, mutant forms of 13245 proteins, fusion proteins, and the like).

20 The recombinant expression vectors of the invention can be designed for expression of 13245 proteins in prokaryotic or eukaryotic cells. For example, polypeptides of the invention can be expressed in *E. coli*, insect cells (e.g., using baculovirus expression vectors), yeast cells or mammalian cells. Suitable host cells are discussed further in Goeddel (1990, *Gene Expression Technology: Methods in Enzymology* 185, Academic Press, San  
25 Diego). Alternatively, the recombinant expression vector can be transcribed and translated in vitro, for example using T7 promoter regulatory sequences and T7 polymerase.

Expression of proteins in prokaryotes is most often carried out in *E. coli* with vectors containing constitutive or inducible promoters directing the expression of either fusion or non-fusion proteins. Fusion vectors add a number of amino acids to a protein encoded  
30 therein, usually to the amino terminus of the recombinant protein. Such fusion vectors typically serve three purposes: 1) to increase expression of recombinant protein; 2) to increase the solubility of the recombinant protein; and 3) to aid in the purification of the recombinant

protein by acting as a ligand in affinity purification. Often, a proteolytic cleavage site is introduced at the junction of the fusion moiety and the recombinant protein to enable separation of the recombinant protein from the fusion moiety subsequent to purification of the fusion protein. Such enzymes, and their cognate recognition sequences, include Factor Xa, thrombin and enterokinase. Typical fusion expression vectors include pGEX (Pharmacia Biotech Inc; Smith et al., 1988, Gene 67:31-40), pMAL (New England Biolabs, Beverly, MA) and pRIT5 (Pharmacia, Piscataway, NJ) which fuse glutathione S-transferase (GST), maltose E binding protein, or protein A, respectively, to the target recombinant protein.

Purified fusion proteins can be used in 13245 activity assays, (e.g., direct assays or competitive assays described in detail below), or to generate antibodies specific for 13245 proteins. In a preferred embodiment, a fusion protein expressed in a retroviral expression vector of the present invention can be used to infect bone marrow cells that are subsequently transplanted into irradiated recipients. The pathology of the subject recipient is then examined after sufficient time has passed (e.g., six weeks).

To maximize recombinant protein expression in *E. coli*, the protein is expressed in a host bacterial strain with an impaired capacity to proteolytically cleave the recombinant protein (Gottesman, 1990, Gene Expression Technology: Methods in Enzymology 185, Academic Press, San Diego, 119-128). Another strategy is to alter the nucleic acid sequence of the nucleic acid to be inserted into an expression vector so that the individual codons for each amino acid are those preferentially utilized in *E. coli* (Wada et al., 1992, Nucl. Acids Res. 20:2111-2118). Such alteration of nucleic acid sequences of the invention can be carried out by standard DNA synthesis techniques.

The 13245 expression vector can be a yeast expression vector, a vector for expression in insect cells, e.g., a baculovirus expression vector, or a vector suitable for expression in mammalian cells.

When used in mammalian cells, the expression vector's control functions are often provided by viral regulatory elements. For example, commonly used viral promoters are derived from polyoma, adenovirus 2, cytomegalovirus and simian virus 40 (SV40).

In another embodiment, the recombinant mammalian expression vector is capable of directing expression of the nucleic acid preferentially in a particular cell type (e.g., tissue-specific regulatory elements are used to express the nucleic acid). Non-limiting examples of suitable tissue-specific promoters include the albumin promoter (liver-specific;

Pinkert et al., 1987, *Genes Dev.* 1:268-277), lymphoid-specific promoters (Calame et al., 1988, *Adv. Immunol.* 43:235-275), in particular promoters of T cell receptors (Winoto et al., 1989, *EMBO J.* 8:729-733) and immunoglobulins (Banerji et al., 1983, *Cell* 33:729-740; Queen et al., 1983, *Cell* 33:741-748), neuron-specific promoters (e.g., the neurofilament promoter; Byrne et al., 1989, *Proc. Natl. Acad. Sci. USA* 86:5473-5477), pancreas-specific promoters (Edlund et al., 1985, *Science* 230:912-916), and mammary gland-specific promoters (e.g., milk whey promoter; U.S. Patent number 4,873,316 and European Patent Application publication number 264,166). Developmentally-regulated promoters are also encompassed, for example, the murine hox promoters (Kessel et al., 1990, *Science* 249:374-379) and the alpha-fetoprotein promoter (Campes et al., 1989, *Genes Dev.* 3:537-546).

The invention further provides a recombinant expression vector comprising a DNA molecule of the invention cloned into the expression vector in an antisense orientation. Regulatory sequences (e.g., viral promoters and/or enhancers) operatively linked to a nucleic acid cloned in the antisense orientation can be chosen which direct the constitutive, tissue specific or cell type specific expression of antisense RNA in a variety of cell types. The antisense expression vector can be in the form of a recombinant plasmid, phagemid or attenuated virus. For a discussion of the regulation of gene expression using antisense genes, see Weintraub, H. et al. (1986, *Trends Genet.* 1:Review).

Another aspect the invention provides a host cell which includes a nucleic acid molecule described herein, e.g., a 13245 nucleic acid molecule within a recombinant expression vector or a 13245 nucleic acid molecule containing sequences which allow it to homologously recombine into a specific site of the host cell's genome. The terms "host cell" and "recombinant host cell" are used interchangeably herein. Such terms refer not only to the particular subject cell, but also to the progeny or potential progeny of such a cell. Because certain modifications can occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are included within the scope of the term as used herein.

A host cell can be any prokaryotic or eukaryotic cell. For example, a 13245 protein can be expressed in bacterial cells such as *E. coli*, insect cells, yeast or mammalian cells (such as Chinese hamster ovary (CHO) cells) or COS cells. Other suitable host cells are known to those skilled in the art.

Vector DNA can be introduced into host cells via conventional transformation or transfection techniques. As used herein, the terms "transformation" and "transfection" are intended to refer to a variety of art-recognized techniques for introducing foreign nucleic acid (e.g., DNA) into a host cell, including calcium phosphate or calcium chloride co-precipitation, DEAE-dextran-mediated transfection, lipofection, or electroporation.

A host cell of the invention can be used to produce (i.e., express) a 13245 protein. Accordingly, the invention further provides methods for producing a 13245 protein using the host cells of the invention. In one embodiment, the method includes culturing the host cell of the invention (into which a recombinant expression vector encoding a 13245 protein has been introduced) in a suitable medium such that a 13245 protein is produced. In another embodiment, the method further includes isolating a 13245 protein from the medium or the host cell.

In another aspect, the invention features, a cell or purified preparation of cells which include a 13245 transgene, or which otherwise mal-express 13245. The cell preparation can consist of human or non-human cells, e.g., rodent cells, e.g., mouse or rat cells, rabbit cells, or pig cells. In preferred embodiments, the cell or cells include a 13245 transgene, e.g., a heterologous form of a 13245, e.g., a gene derived from humans (in the case of a non-human cell). The 13245 transgene can be mal-expressed, e.g., over-expressed or under-expressed. In other preferred embodiments, the cell or cells include a gene that mal-expresses an endogenous 13245, e.g., a gene the expression of which is disrupted, e.g., a knockout. Such cells can serve as a model for studying disorders that are related to mutated or mal-expressed 13245 alleles or for use in drug screening.

In another aspect, the invention includes, a human cell, e.g., a hematopoietic stem cell, transformed with nucleic acid that encodes a subject 13245 polypeptide.

Also provided are cells, preferably human cells, e.g., human hematopoietic or fibroblast cells, in which an endogenous 13245 is under the control of a regulatory sequence that does not normally control expression of the endogenous 13245 gene. The expression characteristics of an endogenous gene within a cell, e.g., a cell line or microorganism, can be modified by inserting a heterologous DNA regulatory element into the genome of the cell such that the inserted regulatory element is operably linked to the endogenous 13245 gene. For example, an endogenous 13245 gene that is "transcriptionally silent," e.g., not normally expressed, or expressed only at very low levels, can be activated by inserting a regulatory

element that is capable of promoting the expression of a normally expressed gene product in that cell. Techniques such as targeted homologous recombination, can be used to insert the heterologous DNA as described (e.g., U.S. Patent number 5,272,071; PCT publication number WO 91/06667).

5

### Transgenic Animals

The invention provides non-human transgenic animals. Such animals are useful for studying the function and/or activity of a 13245 protein and for identifying and/or evaluating modulators of 13245 activity. As used herein, a "transgenic animal" is a non-  
10 human animal, preferably a mammal, more preferably a rodent such as a rat or mouse, in which one or more of the cells of the animal includes a transgene. Other examples of transgenic animals include non-human primates, sheep, dogs, cows, goats, chickens, amphibians, and the like. A transgene is exogenous DNA or a rearrangement, e.g., a deletion of endogenous chromosomal DNA, which preferably is integrated into or occurs in the  
15 genome of the cells of a transgenic animal. A transgene can direct the expression of an encoded gene product in one or more cell types or tissues of the transgenic animal, other transgenes, e.g., a knockout, reduce expression. Thus, a transgenic animal can be one in which an endogenous 13245 gene has been altered, e.g., by homologous recombination between the endogenous gene and an exogenous DNA molecule introduced into a cell of the  
20 animal (e.g., an embryonic cell of the animal, prior to development of the animal).

Intronic sequences and polyadenylation signals can also be included in the transgene to increase the efficiency of expression of the transgene. A tissue-specific regulatory sequence(s) can be operably linked to a transgene of the invention to direct expression of a 13245 protein to particular cells. A transgenic founder animal can be  
25 identified based upon the presence of a 13245 transgene in its genome and/or expression of 13245 mRNA in tissues or cells of the animals. A transgenic founder animal can then be used to breed additional animals carrying the transgene. Moreover, transgenic animals carrying a transgene encoding a 13245 protein can further be bred to other transgenic animals carrying other transgenes.

30 13245 proteins or polypeptides can be expressed in transgenic animals or plants, e.g., a nucleic acid encoding the protein or polypeptide can be introduced into the genome of an animal. In preferred embodiments the nucleic acid is placed under the control

of a tissue specific promoter, e.g., a milk- or egg-specific promoter, and recovered from the milk or eggs produced by the animal. Suitable animals are mice, pigs, cows, goats, and sheep.

The invention also includes a population of cells from a transgenic animal, as discussed, e.g., below.

5

#### Uses

The nucleic acid molecules, proteins, protein homologues, and antibodies described herein can be used in one or more of the following methods: a) screening assays; b) predictive medicine (e.g., diagnostic assays, prognostic assays, monitoring clinical trials, and pharmacogenetics); and c) methods of treatment (e.g., therapeutic and prophylactic). The isolated nucleic acid molecules of the invention can be used, for example, to express a 13245 protein (e.g., via a recombinant expression vector in a host cell in gene therapy applications), to detect a 13245 mRNA (e.g., in a biological sample), to detect a genetic alteration in a 13245 gene and to modulate 13245 activity, as described further below. The 13245 proteins can be used to treat disorders characterized by insufficient or excessive production of a 13245 substrate or production of 13245 inhibitors. In addition, the 13245 proteins can be used to screen for naturally occurring 13245 substrates, to screen for drugs or compounds which modulate 13245 activity, as well as to treat disorders characterized by insufficient or excessive production of 13245 protein or production of 13245 protein forms which have decreased, aberrant or unwanted activity compared to 13245 wild-type protein. Exemplary disorders include those in which protein phosphorylation is aberrant (e.g., muscular and myotonic dystrophies). Moreover, the anti-13245 antibodies of the invention can be used to detect and isolate 13245 proteins, regulate the bioavailability of 13245 proteins, and modulate 13245 activity.

A method of evaluating a compound for the ability to interact with, e.g., bind to, a subject 13245 polypeptide is provided. The method includes: contacting the compound with the subject 13245 polypeptide; and evaluating the ability of the compound to interact with, e.g., to bind or form a complex with, the subject 13245 polypeptide. This method can be performed in vitro, e.g., in a cell free system, or in vivo, e.g., in a two-hybrid interaction trap assay. This method can be used to identify naturally-occurring molecules that interact with a subject 13245 polypeptide. It can also be used to find natural or synthetic inhibitors of a subject 13245 polypeptide. Screening methods are discussed in more detail below.

### Screening Assays

The invention provides screening methods (also referred to herein as "assays") for identifying modulators, i.e., candidate or test compounds or agents (e.g., proteins, peptides, peptidomimetics, peptoids, small molecules or other drugs) which bind with 13245 proteins, have a stimulatory or inhibitory effect on, for example, 13245 expression or 13245 activity, or have a stimulatory or inhibitory effect on, for example, the expression or activity of a 13245 substrate. Compounds thus identified can be used to modulate the activity of target gene products (e.g., 13245 genes) in a therapeutic protocol, to elaborate the biological function of the target gene product, or to identify compounds that disrupt normal target gene interactions.

In one embodiment, the invention provides assays for screening candidate or test compounds that are substrates of a 13245 protein or polypeptide or a biologically active portion thereof. In another embodiment, the invention provides assays for screening candidate or test compounds that bind to or modulate the activity of a 13245 protein or polypeptide or a biologically active portion thereof.

The test compounds of the present invention can be obtained using any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; peptoid libraries (libraries of molecules having the functionalities of peptides, but with a novel, non-peptide backbone which are resistant to enzymatic degradation but which nevertheless remain bioactive; e.g., Zuckermann et al., 1994, J. Med. Chem. 37:2678-2685); spatially addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the 'one-bead one-compound' library method; and synthetic library methods using affinity chromatography selection. The biological library and peptoid library approaches are limited to peptide libraries, while the other four approaches are applicable to peptide, non-peptide oligomer or small molecule libraries of compounds (Lam, 1997, Anticancer Drug Des. 12:145).

Examples of methods for the synthesis of molecular libraries have been described (e.g., DeWitt et al., 1993, Proc. Natl. Acad. Sci. USA 90:6909; Erb et al., 1994, Proc. Natl. Acad. Sci. USA 91:11422; Zuckermann et al., 1994, J. Med. Chem. 37:2678; Cho et al., 1993, Science 261:1303; Carrell et al., 1994, Angew. Chem. Int. Ed. Engl. 33:2059;

Carell et al., 1994, *Angew. Chem. Int. Ed. Engl.* 33:2061; and Gallop et al., 1994, *J. Med. Chem.* 37:1233).

Libraries of compounds can be presented in solution (e.g., Houghten, 1992, *Biotechniques* 13:412-421), or on beads (Lam, 1991, *Nature* 354:82-84), chips (Fodor, 1993, *Nature* 364:555-556), bacteria (U.S. Patent number 5,223,409), spores (U.S. Patent number 5,223,409), plasmids (Cull et al., 1992, *Proc. Natl. Acad. Sci. USA* 89:1865-1869), or on phage (Scott et al., 1990, *Science* 249:386-390; Devlin, 1990, *Science* 249:404-406; Cwirla et al., 1990, *Proc. Natl. Acad. Sci. USA* 87:6378-6382; Felici, 1991, *J. Mol. Biol.* 222:301-310; U.S. Patent number 5,223,409).

In one embodiment, an assay is a cell-based assay in which a cell which expresses a 13245 protein or biologically active portion thereof is contacted with a test compound, and the ability of the test compound to modulate 13245 activity is determined. Determining the ability of the test compound to modulate 13245 activity can be accomplished by monitoring, for example, changes in enzymatic activity. The cell, for example, can be of mammalian origin.

The ability of the test compound to modulate 13245 binding to a compound, e.g., a 13245 substrate, or to bind to 13245 can also be evaluated. This can be accomplished, for example, by coupling the compound, e.g., the substrate, with a radioisotope or enzymatic label such that binding of the compound, e.g., the substrate, to 13245 can be determined by detecting the labeled compound, e.g., substrate, in a complex. Alternatively, 13245 could be coupled with a radioisotope or enzymatic label to monitor the ability of a test compound to modulate 13245 binding to a 13245 substrate in a complex. For example, compounds (e.g., 13245 substrates) can be labeled with  $^{125}\text{I}$ ,  $^{35}\text{S}$ ,  $^{14}\text{C}$ , or  $^3\text{H}$ , either directly or indirectly, and the radioisotope detected by direct counting of radio-emission or by scintillation counting. Alternatively, compounds can be enzymatically labeled with, for example, horseradish peroxidase, alkaline phosphatase, or luciferase, and the enzymatic label detected by determination of conversion of an appropriate substrate to product.

The ability of a compound (e.g., a 13245 substrate) to interact with 13245 with or without the labeling of any of the interactants can be evaluated. For example, a microphysiometer can be used to detect the interaction of a compound with 13245 without the labeling of either the compound or the 13245 (McConnell et al., 1992, *Science* 257:1906-1912). As used herein, a "microphysiometer" (e.g., Cytosensor) is an analytical instrument

that measures the rate at which a cell acidifies its environment using a light-addressable potentiometric sensor (LAPS). Changes in this acidification rate can be used as an indicator of the interaction between a compound and 13245.

In yet another embodiment, a cell-free assay is provided in which a 13245 protein or biologically active portion thereof is contacted with a test compound and the ability of the test compound to bind to the 13245 protein or biologically active portion thereof is evaluated. Preferred biologically active portions of the 13245 proteins to be used in assays of the present invention include fragments that participate in interactions with non-13245 molecules, e.g., fragments with high surface probability scores.

Soluble and/or membrane-bound forms of isolated proteins (e.g., 13245 proteins or biologically active portions thereof) can be used in the cell-free assays of the invention. When membrane-bound forms of the protein are used, it can be desirable to utilize a solubilizing agent. Examples of such solubilizing agents include non-ionic detergents such as n-octylglucoside, n-dodecylglucoside, n-dodecylmaltoside, octanoyl-N-methylglucamide, decanoyl-N-methylglucamide, Triton® X-100, Triton® X-114, Thesit®, Isotridecypoly(ethylene glycol ether)<sub>n</sub>, 3-((3-cholamidopropyl) dimethylamminio)-1-propane sulfonate (CHAPS), 3-((3-cholamidopropyl) dimethylamminio)-2-hydroxy-1-propane sulfonate (CHAPSO), or N-dodecyl-N,N-dimethyl-3-ammonio-1-propane sulfonate.

Cell-free assays involve preparing a reaction mixture of the target gene protein and the test compound under conditions and for a time sufficient to allow the two components to interact and bind, thus forming a complex that can be removed and/or detected.

The interaction between two molecules can also be detected, e.g., using fluorescence energy transfer (FET; e.g., U.S. Patent number 5,631,169; U.S. Patent number 4,868,103). A fluorophore label is selected such that a first donor molecule's emitted fluorescent energy will be absorbed by a fluorescent label on a second, 'acceptor' molecule, which in turn is able to fluoresce due to the absorbed energy. Alternately, the 'donor' protein molecule can simply utilize the natural fluorescent energy of tryptophan residues. Labels are chosen that emit different wavelengths of light, such that the 'acceptor' molecule label can be differentiated from that of the 'donor'. Since the efficiency of energy transfer between the labels is related to the distance separating the molecules, the spatial relationship between the molecules can be assessed. In a situation in which binding occurs between the molecules, the fluorescent emission of the 'acceptor' molecule label in the assay should be maximal. An FET

binding event can be conveniently measured through standard fluorometric detection means well known in the art (e.g., using a fluorimeter).

In another embodiment, determining the ability of the 13245 protein to bind to a target molecule can be accomplished using real-time biomolecular interaction analysis (BIA; e.g., Sjolander et al., 1991, *Anal. Chem.* 63:2338-2345; Szabo et al., 1995, *Curr. Opin. Struct. Biol.* 5:699-705). "Surface plasmon resonance" (SPR) or "BIA" detects biospecific interactions in real time, without labeling any of the interactants (e.g., BIAcore). Changes in the mass at the binding surface (indicative of a binding event) result in alterations of the refractive index of light near the surface (the optical phenomenon of SPR), resulting in a detectable signal that can be used as an indication of real-time reactions between biological molecules.

In one embodiment, the target gene product or the test substance is anchored onto a solid phase. The target gene product/test compound complexes anchored on the solid phase can be detected at the end of the reaction. Preferably, the target gene product can be anchored onto a solid surface, and the test compound, (which is not anchored), can be labeled, either directly or indirectly, with detectable labels discussed herein.

It can be desirable to immobilize either 13245, an anti-13245 antibody or its target molecule to facilitate separation of complexed from non-complexed forms of one or both of the proteins, as well as to accommodate automation of the assay. Binding of a test compound to a 13245 protein, or interaction of a 13245 protein with a target molecule in the presence and absence of a candidate compound, can be accomplished in any vessel suitable for containing the reactants. Examples of such vessels include microtiter plates, test tubes, and micro-centrifuge tubes. In one embodiment, a fusion protein can be provided which adds a domain that allows one or both of the proteins to be bound to a matrix. For example, glutathione-S-transferase/13245 fusion proteins or glutathione-S-transferase/target fusion proteins can be adsorbed onto glutathione Sepharose™ beads (Sigma Chemical, St. Louis, MO) or glutathione-derivatized microtiter plates, which are then combined with the test compound or the test compound and either the non-adsorbed target protein or 13245 protein, and the mixture incubated under conditions conducive for complex formation (e.g., at physiological conditions for salt and pH). Following incubation, the beads or microtiter plate wells are washed to remove any unbound components, the matrix immobilized in the case of beads, complex determined either directly or indirectly, for example, as described above.

Alternatively, the complexes can be dissociated from the matrix, and the level of 13245 binding or activity determined using standard techniques.

Other techniques for immobilizing either a 13245 protein or a target molecule on matrices include using conjugation of biotin and streptavidin. Biotinylated 13245 protein or target molecules can be prepared from biotin- N-hydroxy-succinimide using techniques known in the art (e.g., biotinylation kit, Pierce Chemicals, Rockford, IL), and immobilized in the wells of streptavidin-coated 96 well plates (Pierce Chemical).

In order to conduct the assay, the non-immobilized component is added to the coated surface containing the anchored component. After the reaction is complete, non-reacted components are removed (e.g., by washing) under conditions such that any complexes formed will remain immobilized on the solid surface. The detection of complexes anchored on the solid surface can be accomplished in a number of ways. Where the previously non-immobilized component is pre-labeled, the detection of label immobilized on the surface indicates that complexes were formed. Where the previously non-immobilized component is not pre-labeled, an indirect label can be used to detect complexes anchored on the surface; e.g., using a labeled antibody specific for the immobilized component (the antibody, in turn, can be directly labeled or indirectly labeled with, e.g., a labeled anti-Ig antibody).

In one embodiment, this assay is performed utilizing antibodies reactive with 13245 protein or target molecules but which do not interfere with binding of the 13245 protein to its target molecule. Such antibodies can be derivatized to the wells of the plate, and unbound target or 13245 protein trapped in the wells by antibody conjugation. Methods for detecting such complexes, in addition to those described above for the GST-immobilized complexes, include immunodetection of complexes using antibodies reactive with the 13245 protein or target molecule, as well as enzyme-linked assays which rely on detecting an enzymatic activity associated with the 13245 protein or target molecule.

Alternatively, cell free assays can be conducted in a liquid phase. In such an assay, the reaction products are separated from non-reacted components, by any of a number of standard techniques, including, but not limited to: differential centrifugation (e.g., Rivas et al., 1993, Trends Biochem. Sci. 18:284-287); chromatography (e.g., gel filtration chromatography or ion-exchange chromatography); electrophoresis (e.g., Ausubel et al., eds., 1999, Current Protocols in Molecular Biology, J. Wiley, New York); and immunoprecipitation (e.g., Ausubel, supra). Such resins and chromatographic techniques are

known to one skilled in the art (e.g., Heegaard, 1998, J. Mol. Recognit. 11:141-148; Hage et al., 1997, J. Chromatogr. B Biomed. Sci. Appl. 699:499-525). Further, fluorescence energy transfer can also be conveniently utilized, as described herein, to detect binding without further purification of the complex from solution.

5 In a preferred embodiment, the assay includes contacting the 13245 protein or biologically active portion thereof with a known compound which binds 13245 to form an assay mixture, contacting the assay mixture with a test compound, and determining the ability of the test compound to interact with a 13245 protein, wherein determining the ability of the test compound to interact with a 13245 protein includes determining the ability of the test  
10 compound to preferentially bind to 13245 or biologically active portion thereof, or to modulate the activity of a target molecule, as compared to the known compound.

The target gene products of the invention can, in vivo, interact with one or more cellular or extracellular macromolecules, such as proteins. For the purposes of this discussion, such cellular and extracellular macromolecules are referred to herein as "binding  
15 partners." Compounds that disrupt such interactions can be useful in regulating the activity of the target gene product. Such compounds can include, but are not limited to molecules such as antibodies, peptides, and small molecules. The preferred target genes/products for use in this embodiment are the 13245 genes herein identified. In an alternative embodiment, the invention provides methods for determining the ability of the test compound to modulate the  
20 activity of a 13245 protein through modulation of the activity of a downstream effector of a 13245 target molecule. For example, the activity of the effector molecule on an appropriate target can be determined, or the binding of the effector to an appropriate target can be determined, as previously described.

To identify compounds that interfere with the interaction between the target  
25 gene product and its cellular or extracellular binding partner(s), a reaction mixture containing the target gene product and the binding partner is prepared, under conditions and for a time sufficient, to allow the two products to form complex. In order to test an inhibitory agent, the reaction mixture is provided in the presence and absence of the test compound. The test compound can be initially included in the reaction mixture, or can be added at a time  
30 subsequent to the addition of the target gene and its cellular or extracellular binding partner. Control reaction mixtures are incubated without the test compound or with a placebo. The formation of any complexes between the target gene product and the cellular or extracellular

binding partner is then detected. The formation of a complex in the control reaction, but not in the reaction mixture containing the test compound, indicates that the compound interferes with the interaction of the target gene product and the interactive binding partner.

Additionally, complex formation within reaction mixtures containing the test compound and normal target gene product can also be compared to complex formation within reaction mixtures containing the test compound and mutant target gene product. This comparison can be important in those cases wherein it is desirable to identify compounds that disrupt interactions of mutant but not normal target gene products.

These assays can be conducted in a heterogeneous or homogeneous format.

Heterogeneous assays involve anchoring either the target gene product or the binding partner onto a solid phase, and detecting complexes anchored on the solid phase at the end of the reaction. In homogeneous assays, the entire reaction is carried out in a liquid phase. In either approach, the order of addition of reactants can be varied to obtain different information about the compounds being tested. For example, test compounds that interfere with the interaction between the target gene products and the binding partners, e.g., by competition, can be identified by conducting the reaction in the presence of the test substance. Alternatively, test compounds that disrupt preformed complexes, e.g., compounds with higher binding constants that displace one of the components from the complex, can be tested by adding the test compound to the reaction mixture after complexes have been formed. The various formats are briefly described below.

In a heterogeneous assay system, either the target gene product or the interactive cellular or extracellular binding partner, is anchored onto a solid surface (e.g., a microtiter plate), while the non-anchored species is labeled, either directly or indirectly. The anchored species can be immobilized by non-covalent or covalent attachments. Alternatively, an immobilized antibody specific for the species to be anchored can be used to anchor the species to the solid surface.

In order to conduct the assay, the partner of the immobilized species is exposed to the coated surface with or without the test compound. After the reaction is complete, non-reacted components are removed (e.g., by washing) and any complexes formed will remain immobilized on the solid surface. Where the non-immobilized species is pre-labeled, the detection of label immobilized on the surface indicates that complexes were formed. Where the non-immobilized species is not pre-labeled, an indirect label can be used to detect

complexes anchored on the surface; e.g., using a labeled antibody specific for the initially non-immobilized species (the antibody, in turn, can be directly labeled or indirectly labeled with, e.g., a labeled anti-Ig antibody). Depending upon the order of addition of reaction components, test compounds that inhibit complex formation or that disrupt preformed  
5 complexes can be detected.

Alternatively, the reaction can be conducted in a liquid phase in the presence or absence of the test compound, the reaction products separated from non-reacted components, and complexes detected; e.g., using an immobilized antibody specific for one of the binding components to anchor any complexes formed in solution, and a labeled antibody  
10 specific for the other partner to detect anchored complexes. Again, depending upon the order of addition of reactants to the liquid phase, test compounds that inhibit complex or that disrupt preformed complexes can be identified.

In an alternate embodiment of the invention, a homogeneous assay can be used. For example, a preformed complex of the target gene product and the interactive  
15 cellular or extracellular binding partner product is prepared in that either the target gene products or their binding partners are labeled, but the signal generated by the label is quenched due to complex formation (e.g., U.S. Patent number 4,109,496 that utilizes this approach for immunoassays). The addition of a test substance that competes with and displaces one of the species from the preformed complex will result in the generation of a  
20 signal above background. In this way, test substances that disrupt target gene product-binding partner interaction can be identified.

In yet another aspect, the 13245 proteins can be used as "bait proteins" in a two-hybrid assay or three-hybrid assay (e.g., U.S. Patent number 5,283,317; Zervos et al., 1993, Cell 72:223-232; Madura et al., 1993, J. Biol. Chem. 268:12046-12054; Bartel et al.,  
25 1993, Biotechniques 14:920-924; Iwabuchi et al., 1993, Oncogene 8:1693-1696; PCT publication number WO 94/10300), to identify other proteins, which bind to or interact with 13245 ("13245-binding proteins" or "13245-bp") and are involved in 13245 activity. Such 13245-bps can be activators or inhibitors of signals by the 13245 proteins or 13245 targets as, for example, downstream elements of a 13245-mediated signaling pathway.

30 The two-hybrid system is based on the modular nature of most transcription factors, which consist of separable DNA-binding and activation domains. Briefly, the assay utilizes two different DNA constructs. In one construct, the gene that codes for a 13245

protein is fused to a gene encoding the DNA binding domain of a known transcription factor (e.g., GAL-4). In the other construct, a DNA sequence, from a library of DNA sequences, that encodes an unidentified protein ("prey" or "sample") is fused to a gene that codes for the activation domain of the known transcription factor. (Alternatively, the 13245 protein can be fused to the activator domain). If the "bait" and the "prey" proteins are able to interact in vivo forming a 13245-dependent complex, the DNA-binding and activation domains of the transcription factor are brought into close proximity. This proximity allows transcription of a reporter gene (e.g., LacZ) that is operably linked to a transcriptional regulatory site responsive to the transcription factor. Expression of the reporter gene can be detected and cell colonies containing the functional transcription factor can be isolated and used to obtain the cloned gene that encodes the protein that interacts with the 13245 protein.

In another embodiment, modulators of 13245 expression are identified. For example, a cell or cell free mixture is contacted with a candidate compound and the expression of 13245 mRNA or protein evaluated relative to the level of expression of 13245 mRNA or protein in the absence of the candidate compound. When expression of 13245 mRNA or protein is greater in the presence of the candidate compound than in its absence, the candidate compound is identified as a stimulator of 13245 mRNA or protein expression. Alternatively, when expression of 13245 mRNA or protein is less (i.e., statistically significantly less) in the presence of the candidate compound than in its absence, the candidate compound is identified as an inhibitor of 13245 mRNA or protein expression. The level of 13245 mRNA or protein expression can be determined by methods described herein for detecting 13245 mRNA or protein.

In another aspect, the invention pertains to a combination of two or more of the assays described herein. For example, a modulating agent can be identified using a cell-based or a cell free assay, and the ability of the agent to modulate the activity of a 13245 protein can be confirmed in vivo, e.g., in an animal such as an animal model for a disease.

This invention further pertains to novel agents identified by the above-described screening assays. Accordingly, it is within the scope of this invention to further use an agent identified as described herein (e.g., a 13245 modulating agent, an antisense 13245 nucleic acid molecule, a 13245-specific antibody, or a 13245-binding partner) in an appropriate animal model to determine the efficacy, toxicity, side effects, or mechanism of

action, of treatment with such an agent. Furthermore, novel agents identified by the above-described screening assays can be used for treatments as described herein.

#### Detection Assays

5                   Portions or fragments of the nucleic acid sequences identified herein can be used as polynucleotide reagents. For example, these sequences can be used to: (i) map their respective genes on a chromosome, e.g., to locate gene regions associated with genetic disease or to associate 13245 with a disease; (ii) identify an individual from a minute biological sample (tissue typing); and (iii) aid in forensic identification of a biological sample. These  
10 applications are described in the subsections below.

#### Chromosome Mapping

The 13245 nucleotide sequences or portions thereof can be used to map the location of the 13245 genes on a chromosome. This process is called chromosome mapping.  
15 Chromosome mapping is useful in correlating the 13245 sequences with genes associated with disease.

Briefly, 13245 genes can be mapped to chromosomes by preparing PCR primers (preferably 15-25 base pairs in length) from the 13245 nucleotide sequence (e.g., SEQ ID NO: 1 or SEQ ID NO: 3). These primers can then be used for PCR screening of  
20 somatic cell hybrids containing individual human chromosomes. Only those hybrids containing the human gene corresponding to the 13245 sequences will yield an amplified fragment.

A panel of somatic cell hybrids in which each cell line contains either a single human chromosome or a small number of human chromosomes, and a full set of mouse  
25 chromosomes, can allow easy mapping of individual genes to specific human chromosomes (D'Eustachio et al., 1983, Science 220:919-924).

Other mapping strategies e.g., in situ hybridization as described (Fan et al., 1990, Proc. Natl. Acad. Sci. USA 87:6223-6227), pre-screening with labeled flow-sorted chromosomes, and pre-selection by hybridization to chromosome specific cDNA libraries can  
30 be used to map 13245 to a chromosomal location.

Fluorescence in situ hybridization (FISH) of a DNA sequence to a metaphase chromosomal spread can further be used to provide a precise chromosomal location in one

step. The FISH technique can be used with a DNA sequence as short as 500 or 600 bases. However, clones larger than 1,000 bases have a higher likelihood of binding to a unique chromosomal location with sufficient signal intensity for simple detection. Preferably 1,000 bases, and more preferably 2,000 bases will suffice to get good results at a reasonable amount of time. For a review of FISH, see Verma et al. (1988, Human Chromosomes: A Manual of Basic Techniques, Pergamon Press, New York).

Reagents for chromosome mapping can be used individually to mark a single chromosome or a single site on that chromosome, or panels of reagents can be used for marking multiple sites and/or multiple chromosomes. Reagents corresponding to non-coding regions of the genes are typically preferred for mapping purposes. Coding sequences are more likely to be conserved within gene families, thus increasing the chance of cross hybridizations during chromosomal mapping.

Once a sequence has been mapped to a precise chromosomal location, the physical position of the sequence on the chromosome can be correlated with genetic map data (such data are found, for example, in V. McKusick, Mendelian Inheritance in Man, available on-line through Johns Hopkins University Welch Medical Library). The relationship between a gene and a disease, mapped to the same chromosomal region, can then be identified through linkage analysis (co-inheritance of physically adjacent genes), as described (e.g., Egeland et al., 1987, Nature, 325:783-787).

Moreover, differences in the DNA sequences between individuals affected and unaffected with a disease associated with the 13245 gene, can be determined. If a mutation is observed in some or all of the affected individuals but not in any unaffected individuals, then the mutation is likely to be the causative agent of the particular disease. Comparison of affected and unaffected individuals generally involves first looking for structural alterations in the chromosomes, such as deletions or translocations that are visible from chromosome spreads or detectable using PCR based on that DNA sequence. Ultimately, complete sequencing of genes from several individuals can be performed to confirm the presence of a mutation and to distinguish mutations from polymorphisms.

### Tissue Typing

13245 sequences can be used to identify individuals from biological samples using, e.g., restriction fragment length polymorphism (RFLP). In this technique, an

individual's genomic DNA is digested with one or more restriction enzymes, the fragments separated, e.g., in a Southern blot, and probed to yield bands for identification. The sequences of the present invention are useful as additional DNA markers for RFLP (described in U.S. Patent number 5,272,057).

5 Furthermore, the sequences of the present invention can also be used to determine the actual base-by-base DNA sequence of selected portions of an individual's genome. Thus, the 13245 nucleotide sequence described herein can be used to prepare PCR primers homologous to the 5'- and 3'-ends of the sequence. These primers can then be used to amplify an individual's DNA and subsequently sequence it. Panels of corresponding DNA  
10 sequences from individuals, prepared in this manner, can provide unique individual identifications, as each individual will have a unique set of such DNA sequences due to allelic differences.

Allelic variation occurs to some degree in the coding regions of these sequences, and to a greater degree in the non-coding regions. Each of the sequences  
15 described herein can, to some degree, be used as a standard against which DNA from an individual can be compared for identification purposes. Because greater numbers of polymorphisms occur in the non-coding regions, fewer sequences are necessary to differentiate individuals. The non-coding sequences of SEQ ID NO: 1 can provide positive individual identification with a panel of perhaps 10 to 1,000 primers which each yield a non-  
20 coding amplified sequence of 100 bases. If predicted coding sequences are used, such as those in SEQ ID NO: 3, a more appropriate number of primers for positive individual identification would be 500-2,000.

If a panel of reagents from 13245 nucleotide sequences described herein is used to generate a unique identification database for an individual, those same reagents can  
25 later be used to identify tissue from that individual. Using the unique identification database, positive identification of the individual, living or dead, can be made from extremely small tissue samples.

#### Use of Partial 13245 Sequences in Forensic Biology

30 DNA-based identification techniques can also be used in forensic biology. To make such an identification, PCR technology can be used to amplify DNA sequences taken from very small biological samples such as tissues, e.g., hair or skin, or body fluids, e.g.,

blood, saliva, or semen found at a crime scene. The amplified sequence can then be compared to a standard, thereby allowing identification of the origin of the biological sample.

The sequences of the present invention can be used to provide polynucleotide reagents, e.g., PCR primers, targeted to specific loci in the human genome, which can enhance the reliability of DNA-based forensic identifications by, for example, providing another "identification marker" (i.e., another DNA sequence that is unique to a particular individual). As mentioned above, actual nucleotide sequence information can be used for identification as an accurate alternative to patterns formed by restriction enzyme generated fragments. Sequences targeted to non-coding regions of SEQ ID NO: 1 (e.g., fragments having a length of at least 20 nucleotide residues, preferably at least 30 nucleotide residues) are particularly appropriate for this use.

The 13245 nucleotide sequences described herein can further be used to provide polynucleotide reagents, e.g., labeled or label-able probes which can be used in, for example, an in situ hybridization technique, to identify a specific tissue, e.g., a tissue containing hematopoietic cells. This can be very useful in cases where a forensic pathologist is presented with a tissue of unknown origin. Panels of such 13245 probes can be used to identify tissue by species and/or by organ type.

In a similar fashion, these reagents, e.g., 13245 primers or probes can be used to screen tissue culture for contamination (i.e., to screen for the presence of a mixture of different types of cells in a culture).

#### Predictive Medicine

The present invention also pertains to the field of predictive medicine in which diagnostic assays, prognostic assays, and monitoring clinical trials are used for prognostic (predictive) purposes to thereby treat an individual.

Generally, the invention provides a method of determining if a subject is at risk for a disorder related to a lesion in, or the malexpression of, a gene that encodes a 13245 polypeptide.

Such disorders include, e.g., a disorder associated with the malexpression of a 13245 polypeptide, e.g., an immune disorder or a neoplastic disorder.

The method includes one or more of the following:

(i) detecting, in a tissue of the subject, the presence or absence of a mutation which affects the expression of the 13245 gene, or detecting the presence or absence of a mutation in a region which controls the expression of the gene, e.g., a mutation in the 5'-control region;

(ii) detecting, in a tissue of the subject, the presence or absence of a mutation which alters the structure of the 13245 gene;

(iii) detecting, in a tissue of the subject, the malexpression of the 13245 gene at the mRNA level, e.g., detecting a non-wild-type level of a mRNA; and

(iv) detecting, in a tissue of the subject, the malexpression of the gene at the protein level, e.g., detecting a non-wild-type level of a 13245 polypeptide.

In preferred embodiments the method includes: ascertaining the existence of at least one of: a deletion of one or more nucleotides from the 13245 gene; an insertion of one or more nucleotides into the gene, a point mutation, e.g., a substitution of one or more nucleotides of the gene, a gross chromosomal rearrangement of the gene, e.g., a translocation, inversion, or deletion.

For example, detecting the genetic lesion can include: (i) providing a probe/primer including an oligonucleotide containing a region of nucleotide sequence which hybridizes to a sense or antisense sequence from SEQ ID NO: 1, or naturally occurring mutants thereof, or 5'- or 3'-flanking sequences naturally associated with the 13245 gene; (ii) exposing the probe/primer to nucleic acid of the tissue; and detecting the presence or absence of the genetic lesion by hybridization of the probe/primer to the nucleic acid, e.g., by in situ hybridization.

In preferred embodiments, detecting the malexpression includes ascertaining the existence of at least one of: an alteration in the level of a messenger RNA transcript of the 13245 gene; the presence of a non-wild-type splicing pattern of a messenger RNA transcript of the gene; or a non-wild-type level of 13245 RNA or protein.

Methods of the invention can be used for prenatal screening or to determine if a subject's offspring will be at risk for a disorder.

In preferred embodiments the method includes determining the structure of a 13245 gene, an abnormal structure being indicative of risk for the disorder.

In preferred embodiments the method includes contacting a sample from the subject with an antibody to the 13245 protein or a nucleic acid, which hybridizes specifically with the gene. These and other embodiments are discussed below.

### Diagnostic and Prognostic Assays

The presence, level, or absence of 13245 protein or nucleic acid in a biological sample can be evaluated by obtaining a biological sample from a test subject and contacting the biological sample with a compound or an agent capable of detecting 13245 protein or nucleic acid (e.g., mRNA, genomic DNA) that encodes 13245 protein such that the presence of 13245 protein or nucleic acid is detected in the biological sample. The term "biological sample" includes tissues, cells and biological fluids isolated from a subject, as well as tissues, cells and fluids present within a subject. A preferred biological sample is serum. The level of expression of the 13245 gene can be measured in a number of ways, including, but not limited to: measuring the mRNA encoded by the 13245 genes; measuring the amount of protein encoded by the 13245 genes; or measuring the activity of the protein encoded by the 13245 genes.

The level of mRNA corresponding to the 13245 gene in a cell can be determined both by in situ and by in vitro formats.

The isolated mRNA can be used in hybridization or amplification assays that include, but are not limited to, Southern or Northern analyses, polymerase chain reaction analyses and probe arrays. One preferred diagnostic method for the detection of mRNA levels involves contacting the isolated mRNA with a nucleic acid molecule (probe) that can hybridize to the mRNA encoded by the gene being detected. The nucleic acid probe can be, for example, a full-length 13245 nucleic acid, such as the nucleic acid of SEQ ID NO: 1, or a portion thereof, such as an oligonucleotide of at least 7, 15, 30, 50, 100, 250 or 500 nucleotides in length and sufficient to specifically hybridize under stringent conditions to 13245 mRNA or genomic DNA. Other suitable probes for use in the diagnostic assays are described herein.

In one format, mRNA (or cDNA) is immobilized on a surface and contacted with the probes, for example by running the isolated mRNA on an agarose gel and transferring the mRNA from the gel to a membrane, such as nitrocellulose. In an alternative format, the probes are immobilized on a surface and the mRNA (or cDNA) is contacted with the probes, for example, in a two-dimensional gene chip array. A skilled artisan can adapt known mRNA detection methods for use in detecting the level of mRNA encoded by the 13245 genes.

The level of mRNA in a sample that is encoded by 13245 can be evaluated with nucleic acid amplification, e.g., by RT-PCR (U.S. Patent number 4,683,202), ligase chain reaction (Barany, 1991, Proc. Natl. Acad. Sci. USA 88:189-193), self-sustained sequence replication (Guatelli et al., 1990, Proc. Natl. Acad. Sci. USA 87:1874-1878), transcriptional amplification system (Kwoh et al., 1989, Proc. Natl. Acad. Sci. USA 86:1173-1177), Q-Beta Replicase (Lizardi et al., 1988, Bio/Technology 6:1197), rolling circle replication (U.S. Patent number 5,854,033) or any other nucleic acid amplification method, followed by the detection of the amplified molecules using techniques known in the art. As used herein, amplification primers are defined as being a pair of nucleic acid molecules that can anneal to 5'- or 3'-regions of a 13245 gene (plus and minus strands, respectively, or vice-versa) and contain a short region in between. In general, amplification primers are from about 10 to 30 nucleotides in length and flank a region from about 50 to 200 nucleotides in length. Under appropriate conditions and with appropriate reagents, such primers permit the amplification of a nucleic acid molecule comprising the nucleotide sequence between the primers.

For in situ methods, a cell or tissue sample can be prepared/processed and immobilized on a support, typically a glass slide, and then contacted with a probe that can hybridize to mRNA that encodes the 13245 gene being analyzed.

In another embodiment, the methods include further contacting a control sample with a compound or agent capable of detecting 13245 mRNA, or genomic DNA, and comparing the presence of 13245 mRNA or genomic DNA in the control sample with the presence of 13245 mRNA or genomic DNA in the test sample.

A variety of methods can be used to determine the level of protein encoded by 13245. In general, these methods include contacting an agent that selectively binds to the protein, such as an antibody with a sample, to evaluate the level of protein in the sample. In a preferred embodiment, the antibody bears a detectable label. Antibodies can be polyclonal, or more preferably, monoclonal. An intact antibody, or a fragment thereof (e.g., Fab or F(ab')<sub>2</sub>) can be used. The term "labeled," with regard to the probe or antibody, is intended to encompass direct labeling of the probe or antibody by coupling (i.e., physically linking) a detectable substance to the probe or antibody, as well as indirect labeling of the probe or antibody by reactivity with a detectable substance. Examples of detectable substances are provided herein.

The detection methods can be used to detect 13245 protein in a biological sample in vitro as well as in vivo. In vitro techniques for detection of 13245 protein include enzyme linked immunosorbent assays (ELISAs), immunoprecipitations, immunofluorescence, enzyme immunoassay (EIA), radioimmunoassay (RIA), and Western blot analysis. In vivo techniques for detection of 13245 protein include introducing into a subject a labeled anti-13245 antibody. For example, the antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques.

In another embodiment, the methods further include contacting the control sample with a compound or agent capable of detecting 13245 protein, and comparing the presence of 13245 protein in the control sample with the presence of 13245 protein in the test sample.

The invention also includes kits for detecting the presence of 13245 in a biological sample. For example, the kit can include a compound or agent capable of detecting 13245 protein or mRNA in a biological sample, and a standard. The compound or agent can be packaged in a suitable container. The kit can further comprise instructions for using the kit to detect 13245 protein or nucleic acid.

For antibody-based kits, the kit can include: (1) a first antibody (e.g., attached to a solid support) which binds to a polypeptide corresponding to a marker of the invention; and, optionally, (2) a second, different antibody which binds to either the polypeptide or the first antibody and is conjugated to a detectable agent.

For oligonucleotide-based kits, the kit can include: (1) an oligonucleotide, e.g., a detectably-labeled oligonucleotide, which hybridizes to a nucleic acid sequence encoding a polypeptide corresponding to a marker of the invention or (2) a pair of primers useful for amplifying a nucleic acid molecule corresponding to a marker of the invention. The kit can also include a buffering agent, a preservative, or a protein-stabilizing agent. The kit can also include components necessary for detecting the detectable agent (e.g., an enzyme or a substrate). The kit can also contain a control sample or a series of control samples that can be assayed and compared to the test sample contained. Each component of the kit can be enclosed within an individual container and all of the various containers can be within a single package, along with instructions for interpreting the results of the assays performed using the kit.

The diagnostic methods described herein can identify subjects having, or at risk of developing, a disease or disorder associated with malexpressed, aberrant or unwanted 13245 expression or activity. As used herein, the term "unwanted" includes an unwanted phenomenon involved in a biological response such as induction of an inappropriate immune response or deregulated cell proliferation.

In one embodiment, a disease or disorder associated with aberrant or unwanted 13245 expression or activity is identified. A test sample is obtained from a subject and 13245 protein or nucleic acid (e.g., mRNA or genomic DNA) is evaluated, wherein the level, e.g., the presence or absence, of 13245 protein or nucleic acid is diagnostic for a subject having or at risk of developing a disease or disorder associated with aberrant or unwanted 13245 expression or activity. As used herein, a "test sample" refers to a biological sample obtained from a subject of interest, including a biological fluid (e.g., serum), cell sample, or tissue.

The prognostic assays described herein can be used to determine whether a subject can be administered an agent (e.g., an agonist, antagonist, peptidomimetic, protein, peptide, nucleic acid, small molecule, or other drug candidate) to treat a disease or disorder associated with aberrant or unwanted 13245 expression or activity. For example, such methods can be used to determine whether a subject can be effectively treated with an agent that modulates 13245 expression or activity.

The methods of the invention can also be used to detect genetic alterations in a 13245 gene, thereby determining if a subject with the altered gene is at risk for a disorder characterized by misregulation in 13245 protein activity or nucleic acid expression, such as a disorder associated with tumorigenesis or induction of an inappropriate immune response. In preferred embodiments, the methods include detecting, in a sample from the subject, the presence or absence of a genetic alteration characterized by at least one of an alteration affecting the integrity of a gene encoding a 13245 protein, or the malexpression of the 13245 gene. For example, such genetic alterations can be detected by ascertaining the existence of at least one of 1) a deletion of one or more nucleotides from a 13245 gene; 2) an addition of one or more nucleotides to a 13245 gene; 3) a substitution of one or more nucleotides of a 13245 gene, 4) a chromosomal rearrangement of a 13245 gene; 5) an alteration in the level of a messenger RNA transcript of a 13245 gene, 6) aberrant modification of a 13245 gene, such as of the methylation pattern of the genomic DNA, 7) the presence of a non-wild-type splicing pattern of a messenger RNA transcript of a 13245 gene, 8) a non-wild-type level of a 13245

protein, 9) allelic loss of a 13245 gene, and 10) inappropriate post-translational modification of a 13245 protein.

An alteration can be detected without a probe/primer in a polymerase chain reaction, such as anchor PCR or RACE-PCR, or, alternatively, in a ligation chain reaction (LCR), the latter of which can be particularly useful for detecting point mutations in the 13245 gene. This method can include the steps of collecting a sample of cells from a subject, isolating nucleic acid (e.g., genomic, mRNA or both) from the sample, contacting the nucleic acid sample with one or more primers which specifically hybridize to a 13245 gene under conditions such that hybridization and amplification of the 13245 gene occurs (if present), and detecting the presence or absence of an amplification product, or detecting the size of the amplification product and comparing the length to a control sample. It is anticipated that PCR and/or LCR can be desirable to use as a preliminary amplification step in conjunction with any of the techniques used for detecting mutations described herein.

Alternative amplification methods include: self sustained sequence replication (Guatelli et al., 1990, Proc. Natl. Acad. Sci. USA 87:1874-1878), transcriptional amplification system (Kwoh et al., 1989, Proc. Natl. Acad. Sci. USA 86:1173-1177), Q-Beta Replicase (Lizardi et al., 1988, Bio/Technology 6:1197), or other nucleic acid amplification methods, followed by the detection of the amplified molecules using techniques known to those of skill in the art.

In another embodiment, mutations in a 13245 gene from a sample cell can be identified by detecting alterations in restriction enzyme cleavage patterns. For example, sample and control DNA is isolated, amplified (optionally), digested with one or more restriction endonucleases, and fragment length sizes are determined, e.g., by gel electrophoresis, and compared. Differences in fragment length sizes between sample and control DNA indicates mutations in the sample DNA. Moreover, the use of sequence specific ribozymes (e.g., U.S. Patent number 5,498,531) can be used to score for the presence of specific mutations by development or loss of a ribozyme cleavage site.

In other embodiments, genetic mutations in 13245 can be identified by hybridizing a sample to control nucleic acids, e.g., DNA or RNA, by, e.g., two-dimensional arrays, or, e.g., chip based arrays. Such arrays include a plurality of addresses, each of which is positionally distinguishable from the other. A different probe is located at each address of the plurality. The arrays can have a high density of addresses, e.g., can contain hundreds or

thousands of oligonucleotides probes (Cronin et al., 1996, Hum. Mutat. 7:244-255; Kozal et al., 1996, Nature Med. 2:753-759). For example, genetic mutations in 13245 can be identified in two-dimensional arrays containing light-generated DNA probes as described (Cronin et al., supra). Briefly, a first hybridization array of probes can be used to scan through long stretches of DNA in a sample and control to identify base changes between the sequences by making linear arrays of sequential overlapping probes. This step allows the identification of point mutations. This step is followed by a second hybridization array that allows the characterization of specific mutations by using smaller, specialized probe arrays complementary to all variants or mutations detected. Each mutation array is composed of parallel probe sets, one complementary to the wild-type gene and the other complementary to the mutant gene.

In yet another embodiment, any of a variety of sequencing reactions known in the art can be used to directly sequence the 13245 gene and detect mutations by comparing the sequence of the sample 13245 with the corresponding wild-type (control) sequence.

Automated sequencing procedures can be utilized when performing the diagnostic assays (1995, Biotechniques 19:448), including sequencing by mass spectrometry.

Other methods for detecting mutations in the 13245 gene include methods in which protection from cleavage agents is used to detect mismatched bases in RNA/RNA or RNA/DNA heteroduplexes (Myers et al., 1985, Science 230:1242; Cotton et al., 1988, Proc. Natl. Acad. Sci. USA 85:4397; Saleeba et al., 1992, Meth. Enzymol. 217:286-295).

In still another embodiment, the mismatch cleavage reaction employs one or more proteins that recognize mismatched base pairs in double-stranded DNA (so called "DNA mismatch repair" enzymes) in defined systems for detecting and mapping point mutations in 13245 cDNAs obtained from samples of cells. For example, the mutY enzyme of E. coli cleaves A at G/A mismatches and the thymidine DNA glycosylase from HeLa cells cleaves T at G/T mismatches (Hsu et al., 1994, Carcinogenesis 15:1657-1662; U.S. Patent number 5,459,039).

In other embodiments, alterations in electrophoretic mobility will be used to identify mutations in 13245 genes. For example, single strand conformation polymorphism (SSCP) can be used to detect differences in electrophoretic mobility between mutant and wild-type nucleic acids (Orita et al., 1989, Proc. Natl. Acad. Sci. USA 86:2766; Cotton, 1993, Mutat. Res. 285:125-144; Hayashi, 1992, Genet. Anal. Tech. Appl. 9:73-79). Single-stranded

DNA fragments of sample and control 13245 nucleic acids will be denatured and allowed to re-nature. The secondary structure of single-stranded nucleic acids varies according to sequence, the resulting alteration in electrophoretic mobility enables the detection of even a single base change. The DNA fragments can be labeled or detected with labeled probes. The sensitivity of the assay can be enhanced by using RNA (rather than DNA), in which the secondary structure is more sensitive to a change in sequence. In a preferred embodiment, the subject method utilizes heteroduplex analysis to separate double stranded heteroduplex molecules on the basis of changes in electrophoretic mobility (Keen et al., 1991, Trends Genet 7:5).

In yet another embodiment, the movement of mutant or wild-type fragments in polyacrylamide gels containing a gradient of denaturant is assayed using denaturing gradient gel electrophoresis (DGGE) (Myers et al., 1985, Nature 313:495). When DGGE is used as the method of analysis, DNA will be modified to insure that it does not completely denature, for example by adding a GC clamp of approximately 40 base pairs of high-melting GC-rich DNA by PCR. In a further embodiment, a temperature gradient is used in place of a denaturing gradient to identify differences in the mobility of control and sample DNA (Rosenbaum and Reissner (1987) Biophys Chem 265:12753).

Examples of other techniques for detecting point mutations include, but are not limited to, selective oligonucleotide hybridization, selective amplification, or selective primer extension (Saiki et al., 1986, Nature 324:163; Saiki et al., 1989, Proc. Natl. Acad. Sci. USA 86:6230).

Alternatively, allele specific amplification technology that depends on selective PCR amplification can be used in conjunction with the instant invention. Oligonucleotides used as primers for specific amplification can carry the mutation of interest in the center of the molecule (so that amplification depends on differential hybridization; Gibbs et al., 1989, Nucl. Acids Res. 17:2437-2448) or at the extreme 3'-end of one primer where, under appropriate conditions, mismatch can prevent, or reduce polymerase extension (Prossner, 1993, Tibtech 11:238). In addition, it can be desirable to introduce a novel restriction site in the region of the mutation to create cleavage-based detection (Gasparini et al., 1992, Mol. Cell Probes 6:1). It is anticipated that in certain embodiments, amplification can also be performed using Taq ligase for amplification (Barany, 1991, Proc. Natl. Acad. Sci. USA 88:189). In such cases, ligation will occur only if there is a perfect match at the 3'-

end of the 5'- sequence making it possible to detect the presence of a known mutation at a specific site by looking for the presence or absence of amplification.

The methods described herein can be performed, for example, using pre-packaged diagnostic kits comprising at least one probe nucleic acid or antibody reagent described herein, which can be conveniently used, e.g., in clinical settings to diagnose patients exhibiting symptoms or family history of a disease or illness involving a 13245 gene.

#### Use of 13245 Molecules as Surrogate Markers

The 13245 molecules of the invention are also useful as markers of disorders or disease states, as markers for precursors of disease states, as markers for predisposition of disease states, as markers of drug activity, or as markers of the pharmacogenomic profile of a subject. Using the methods described herein, the presence, absence and/or quantity of the 13245 molecules of the invention can be detected, and can be correlated with one or more biological states in vivo. For example, the 13245 molecules of the invention can serve as surrogate markers for one or more disorders or disease states or for conditions leading up to disease states. As used herein, a "surrogate marker" is an objective biochemical marker which correlates with the absence or presence of a disease or disorder, or with the progression of a disease or disorder (e.g., with the presence or absence of a tumor). The presence or quantity of such markers is independent of the disease. Therefore, these markers can serve to indicate whether a particular course of treatment is effective in lessening a disease state or disorder. Surrogate markers are of particular use when the presence or extent of a disease state or disorder is difficult to assess through standard methodologies (e.g., early stage tumors), or when an assessment of disease progression is desired before a potentially dangerous clinical endpoint is reached (e.g., an assessment of cardiovascular disease can be made using cholesterol levels as a surrogate marker, and an analysis of HIV infection can be made using HIV RNA levels as a surrogate marker, well in advance of the undesirable clinical outcomes of myocardial infarction or fully-developed AIDS). Examples of the use of surrogate markers have been described (e.g., Koomen et al., 2000, J. Mass. Spectrom. 35:258-264; James, 1994, AIDS Treat. News Arch. 209).

The 13245 molecules of the invention are also useful as pharmacodynamic markers. As used herein, a "pharmacodynamic marker" is an objective biochemical marker which correlates specifically with drug effects. The presence or quantity of a

pharmacodynamic marker is not related to the disease state or disorder for which the drug is being administered; therefore, the presence or quantity of the marker is indicative of the presence or activity of the drug in a subject. For example, a pharmacodynamic marker can be indicative of the concentration of the drug in a biological tissue, in that the marker is either expressed or transcribed or not expressed or transcribed in that tissue in relationship to the level of the drug. In this fashion, the distribution or uptake of the drug can be monitored by the pharmacodynamic marker. Similarly, the presence or quantity of the pharmacodynamic marker can be related to the presence or quantity of the metabolic product of a drug, such that the presence or quantity of the marker is indicative of the relative breakdown rate of the drug in vivo. Pharmacodynamic markers are of particular use in increasing the sensitivity of detection of drug effects, particularly when the drug is administered in low doses. Since even a small amount of a drug can be sufficient to activate multiple rounds of marker (e.g., a 13245 marker) transcription or expression, the amplified marker can be in a quantity which is more readily detectable than the drug itself. Also, the marker can be more easily detected due to the nature of the marker itself; for example, using the methods described herein, anti-13245 antibodies can be employed in an immune-based detection system for a 13245 protein marker, or 13245-specific radiolabeled probes can be used to detect a 13245 mRNA marker. Furthermore, the use of a pharmacodynamic marker can offer mechanism-based prediction of risk due to drug treatment beyond the range of possible direct observations. Examples of the use of pharmacodynamic markers have been described (e.g., U.S. Patent number 6,033,862; Hattis et al., 1991, *Env. Health Perspect.* 90: 229-238; Schentag, 1999, *Am. J. Health-Syst. Pharm.* 56 Suppl. 3: S21-S24; Nicolau, 1999, *Am. J. Health-Syst. Pharm.* 56 Suppl. 3: S16-S20).

The 13245 molecules of the invention are also useful as pharmacogenomic markers. As used herein, a "pharmacogenomic marker" is an objective biochemical marker which correlates with a specific clinical drug response or susceptibility in a subject (e.g., McLeod et al., 1999, *Eur. J. Cancer* 35:1650-1652). The presence or quantity of the pharmacogenomic marker is related to the predicted response of the subject to a specific drug or class of drugs prior to administration of the drug. By assessing the presence or quantity of one or more pharmacogenomic markers in a subject, a drug therapy which is most appropriate for the subject, or which is predicted to have a greater degree of success, can be selected. For example, based on the presence or quantity of RNA, or protein (e.g., 13245 protein or RNA)

for specific tumor markers in a subject, a drug or course of treatment can be selected that is optimized for the treatment of the specific tumor likely to be present in the subject. Similarly, the presence or absence of a specific sequence mutation in 13245 DNA can correlate 13245 drug response. The use of pharmacogenomic markers therefore permits the application of the most appropriate treatment for each subject without having to administer the therapy.

### Pharmaceutical Compositions

The nucleic acid and polypeptides, fragments thereof, as well as anti-13245 antibodies (also referred to herein as "active compounds") of the invention can be incorporated into pharmaceutical compositions. Such compositions typically include the nucleic acid molecule, protein, or antibody and a pharmaceutically acceptable carrier. As used herein the language "pharmaceutically acceptable carrier" includes solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. Supplementary active compounds can also be incorporated into the compositions.

A pharmaceutical composition is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, e.g., intravenous, intradermal, subcutaneous, oral (e.g., inhalation), transdermal (topical), transmucosal, and rectal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF,

Parsippany, NJ) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringability exists. It should be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including an agent in the composition that delays absorption, for example, aluminium monostearate and gelatin.

Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying, which yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Oral compositions generally include an inert diluent or an edible carrier. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules, e.g., gelatin capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash.

Pharmaceutically compatible binding agents and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder, such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient, such as starch or lactose; a disintegrating

agent, such as alginic acid, Primogel™, or corn starch; a lubricant, such as magnesium stearate or Sterotes™; a glidant, such as colloidal silicon dioxide; a sweetening agent, such as sucrose or saccharin; or a flavoring agent, such as peppermint, methyl salicylate, or orange flavoring.

5 For administration by inhalation, the compounds are delivered in the form of an aerosol spray from pressured container or dispenser that contains a suitable propellant, e.g., a gas such as carbon dioxide, or a nebulizer.

Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be  
10 permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

15 The compounds can also be prepared in the form of suppositories (e.g., with conventional suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery.

In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release  
20 formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal  
25 suspensions (including liposomes targeted to infected cells using monoclonal antibodies directed towards viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to described methods (e.g., U.S. Patent number 4,522,811).

It is advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein  
30 refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier.

Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD<sub>50</sub> (the dose lethal to 50% of the population) and the ED<sub>50</sub> (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD<sub>50</sub>/ED<sub>50</sub>. Compounds that exhibit high therapeutic indices are preferred. While compounds that exhibit toxic side effects can be used, care should be taken to design a delivery system that targets such compounds to the site of affected tissue in order to minimize potential damage to uninfected cells and, thereby, reduce side effects.

The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED<sub>50</sub> with little or no toxicity. The dosage can vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound used in the method of the invention, the therapeutically effective dose can be estimated initially from cell culture assays. A dose can be formulated in animal models to achieve a circulating plasma concentration range that includes the IC<sub>50</sub> (i.e., the concentration of the test compound which achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma can be measured, for example, by high performance liquid chromatography.

As defined herein, a therapeutically effective amount of protein or polypeptide (i.e., an effective dosage) ranges from about 0.001 to 30 milligrams per kilogram body weight, preferably about 0.01 to 25 milligrams per kilogram body weight, more preferably about 0.1 to 20 milligrams per kilogram body weight, and even more preferably about 1 to 10 milligrams per kilogram, 2 to 9 milligrams per kilogram, 3 to 8 milligrams per kilogram, 4 to 7 milligrams per kilogram, or 5 to 6 milligrams per kilogram body weight. The protein or polypeptide can be administered one time per week for between about 1 to 10 weeks, preferably between 2 to 8 weeks, more preferably between about 3 to 7 weeks, and even more preferably for about 4, 5, or 6 weeks. The skilled artisan will appreciate that certain factors can influence the dosage and timing required to effectively treat a subject, including but not limited to the severity of the disease or disorder, previous treatments, the general health and/or age of the subject, and other diseases present. Moreover, treatment of a subject with a

therapeutically effective amount of a protein, polypeptide, or antibody can include a single treatment or, preferably, can include a series of treatments.

For antibodies, the preferred dosage is 0.1 milligrams per kilogram of body weight (generally 10 to 20 milligrams per kilogram). If the antibody is to act in the brain, a dosage of 50 to 100 milligrams per kilogram is usually appropriate. Generally, partially human antibodies and fully human antibodies have a longer half-life within the human body than other antibodies. Accordingly, lower dosages and less frequent administration is often possible. Modifications such as lipidation can be used to stabilize antibodies and to enhance uptake and tissue penetration (e.g., into the brain). A method for the lipidation of antibodies is described by Cruikshank et al. (1997, J. AIDS Hum. Retrovir. 14:193).

The present invention encompasses agents that modulate expression or activity. An agent may, for example, be a small molecule. For example, such small molecules include, but are not limited to, peptides, peptidomimetics (e.g., peptoids), amino acids, amino acid analogs, polynucleotides, polynucleotide analogs, nucleotides, nucleotide analogs, organic or inorganic compounds (i.e., including hetero-organic and organo-metallic compounds) having a molecular weight less than about 10,000 grams per mole, organic or inorganic compounds having a molecular weight less than about 5,000 grams per mole, organic or inorganic compounds having a molecular weight less than about 1,000 grams per mole, organic or inorganic compounds having a molecular weight less than about 500 grams per mole, and salts, esters, and other pharmaceutically acceptable forms of such compounds.

Exemplary doses include milligram or microgram amounts of the small molecule per kilogram of subject or sample weight (e.g., about 1 microgram per kilogram to about 500 milligrams per kilogram, about 100 micrograms per kilogram to about 5 milligrams per kilogram, or about 1 microgram per kilogram to about 50 micrograms per kilogram. It is furthermore understood that appropriate doses of a small molecule depend upon the potency of the small molecule with respect to the expression or activity to be modulated. When one or more of these small molecules is to be administered to an animal (e.g., a human) in order to modulate expression or activity of a polypeptide or nucleic acid of the invention, a physician, veterinarian, or researcher may, for example, prescribe a relatively low dose at first, subsequently increasing the dose until an appropriate response is obtained. In addition, it is understood that the specific dose level for any particular animal subject will depend upon a variety of factors including the activity of the specific compound employed, the age, body

weight, general health, gender, and diet of the subject, the time of administration, the route of administration, the rate of excretion, any drug combination, and the degree of expression or activity to be modulated.

An antibody (or fragment thereof) can be conjugated to a therapeutic moiety  
5 such as a cytotoxin, a therapeutic agent or a radioactive metal ion. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include taxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, teniposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine,  
10 lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and  
15 cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (e.g., vincristine and vinblastine).

The conjugates of the invention can be used for modifying a given biological  
20 response, and the drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety can be a protein or polypeptide possessing a desired biological activity. Such proteins can include, for example, a toxin such as abrin, ricin A, gelonin, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor, alpha-interferon, beta-interferon, nerve growth factor, platelet derived growth factor,  
25 tissue plasminogen activator; or, biological response modifiers such as, for example, lymphokines, interleukins-1, -2, and -6, granulocyte macrophage colony stimulating factor, granulocyte colony stimulating factor, or other growth factors.

Alternatively, an antibody can be conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S. Patent number 4,676,980.

30 The nucleic acid molecules of the invention can be inserted into vectors and used as gene therapy vectors. Gene therapy vectors can be delivered to a subject by, for example, intravenous injection, local administration (see U.S. Patent number 5,328,470) or by

stereotactic injection (e.g., Chen et al., 1994, Proc. Natl. Acad. Sci. USA 91:3054-3057). The pharmaceutical preparation of the gene therapy vector can include the gene therapy vector in an acceptable diluent, or can comprise a slow release matrix in which the gene delivery vehicle is imbedded. Alternatively, where the complete gene delivery vector can be produced intact from recombinant cells, e.g., retroviral vectors, the pharmaceutical preparation can include one or more cells which produce the gene delivery system.

The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

## Methods of Treatment

The present invention provides for both prophylactic and therapeutic methods of treating a subject at risk of (or susceptible to) a disorder or having a disorder associated with aberrant or unwanted expression or activity. With regards to both prophylactic and therapeutic methods of treatment, such treatments can be specifically tailored or modified, based on knowledge obtained from the field of pharmacogenomics.

"Pharmacogenomics," as used herein, refers to the application of genomics technologies such as gene sequencing, statistical genetics, and gene expression analysis to drugs in clinical development and on the market. More specifically, the term refers the study of how a patient's genes determine his or her response to a drug (e.g., a patient's "drug response phenotype," or "drug response genotype".) Thus, another aspect of the invention provides methods for tailoring an individual's prophylactic or therapeutic treatment with either the molecules of the present invention or modulators according to that individual's drug response genotype. Pharmacogenomics allows a clinician or physician to target prophylactic or therapeutic treatments to patients who will most benefit from the treatment and to avoid treatment of patients who will experience toxic drug-related side effects.

Treatment is defined as the application or administration of a therapeutic agent to a patient, or application or administration of a therapeutic agent to an isolated tissue or cell line from a patient, who has a disease, a symptom of disease or a predisposition toward a disease, with the purpose to cure, heal, alleviate, relieve, alter, remedy, ameliorate, improve or affect the disease, the symptoms of disease or the predisposition toward disease.

A therapeutic agent includes, but is not limited to, small molecules, peptides, antibodies, ribozymes and antisense oligonucleotides.

In one aspect, the invention provides a method for preventing a disease or condition in a subject associated with an aberrant or unwanted 13245 expression or activity, by administering to the subject a 13245 or an agent which modulates 13245 expression, or at least one 13245 activity. Subjects at risk for a disease which is caused or contributed to by aberrant or unwanted 13245 expression or activity can be identified by, for example, any or a combination of diagnostic or prognostic assays as described herein. Administration of a prophylactic agent can occur prior to the manifestation of symptoms characteristic of the 13245 aberrance, such that a disease or disorder is prevented or, alternatively, delayed in its progression. Depending on the type of 13245 aberrance, for example, a 13245 protein, 13245 agonist or 13245 antagonist agent can be used for treating the subject. The appropriate agent can be determined based on screening assays described herein.

It is possible that some 13245 disorders can be caused, at least in part, by an abnormal level of gene product, or by the presence of a gene product exhibiting abnormal activity. As such, the reduction in the level and/or activity of such gene products would bring about the amelioration of disorder symptoms.

As discussed, successful treatment of 13245 disorders can be brought about by techniques that serve to inhibit the expression or activity of target gene products. For example, compounds, e.g., an agent identified using an assays described above, that proves to exhibit negative modulatory activity, can be used in accordance with the invention to prevent and/or ameliorate symptoms of 13245 disorders. Such molecules can include, but are not limited to peptides, phosphopeptides, small organic or inorganic molecules, or antibodies (including, for example, polyclonal, monoclonal, humanized, anti-idiotypic, chimeric or single chain antibodies, and Fab, F(ab')<sub>2</sub> and Fab expression library fragments, scFV molecules, and epitope-binding fragments thereof).

Further, antisense and ribozyme molecules that inhibit expression of the target gene can also be used in accordance with the invention to reduce the level of target gene expression, thus effectively reducing the level of target gene activity. Still further, triple helix molecules can be utilized in reducing the level of target gene activity. Antisense, ribozyme and triple helix molecules are discussed above.

It is possible that the use of antisense, ribozyme, and/or triple helix molecules to reduce or inhibit mutant gene expression can also reduce or inhibit the transcription (triple helix) and/or translation (antisense, ribozyme) of mRNA produced by normal target gene

alleles, such that the concentration of normal target gene product present can be lower than is necessary for a normal phenotype. In such cases, nucleic acid molecules that encode and express target gene polypeptides exhibiting normal target gene activity can be introduced into cells via gene therapy method. Alternatively, in instances in that the target gene encodes an extracellular protein, it can be preferable to co-administer normal target gene protein into the cell or tissue in order to maintain the requisite level of cellular or tissue target gene activity.

Another method by which nucleic acid molecules can be utilized in treating or preventing a disease characterized by 13245 expression is through the use of aptamer molecules specific for 13245 protein. Aptamers are nucleic acid molecules having a tertiary structure that permits them to specifically bind to protein ligands (e.g., Osborne et al., 1997, Curr. Opin. Chem. Biol. 1:5-9; Patel, 1997, Curr. Opin. Chem. Biol. 1:32-46). Since nucleic acid molecules can in many cases be more conveniently introduced into target cells than therapeutic protein molecules can be, aptamers offer a method by which 13245 protein activity can be specifically decreased without the introduction of drugs or other molecules which can have pluripotent effects.

Antibodies can be generated that are both specific for target gene product and that reduce target gene product activity. Such antibodies may, therefore, be administered in instances whereby negative modulatory techniques are appropriate for the treatment of 13245 disorders.

In circumstances wherein injection of an animal or a human subject with a 13245 protein or epitope for stimulating antibody production is harmful to the subject, it is possible to generate an immune response against 13245 through the use of anti-idiotypic antibodies (e.g., Herlyn, 1999, Ann. Med. 31:66-78; Bhattacharya-Chatterjee et al., 1998, Cancer Treat. Res. 94:51-68). If an anti-idiotypic antibody is introduced into a mammal or human subject, it should stimulate the production of anti-anti-idiotypic antibodies, which should be specific to the 13245 protein. Vaccines directed to a disease characterized by 13245 expression can also be generated in this fashion.

In instances where the target antigen is intracellular and whole antibodies are used, internalizing antibodies can be preferred. Lipofectin or liposomes can be used to deliver the antibody or a fragment of the Fab region that binds to the target antigen into cells. Where fragments of the antibody are used, the smallest inhibitory fragment that binds to the target antigen is preferred. For example, peptides having an amino acid sequence corresponding to

the Fv region of the antibody can be used. Alternatively, single chain neutralizing antibodies that bind to intracellular target antigens can also be administered. Such single chain antibodies can be administered, for example, by expressing nucleotide sequences encoding single-chain antibodies within the target cell population (e.g., Marasco et al., 1993, Proc. Natl. Acad. Sci. USA 90:7889-7893).

The identified compounds that inhibit target gene expression, synthesis and/or activity can be administered to a patient at therapeutically effective doses to prevent, treat or ameliorate disorders. A therapeutically effective dose refers to that amount of the compound sufficient to result in amelioration of symptoms of the disorders.

Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD<sub>50</sub> (the dose lethal to 50% of the population) and the ED<sub>50</sub> (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD<sub>50</sub>/ED<sub>50</sub>. Compounds that exhibit large therapeutic indices are preferred. While compounds that exhibit toxic side effects can be used, care should be taken to design a delivery system that targets such compounds to the site of affected tissue in order to minimize potential damage to uninfected cells and, thereby, reduce side effects.

The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED<sub>50</sub> with little or no toxicity. The dosage can vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound used in the method of the invention, the therapeutically effective dose can be estimated initially from cell culture assays. A dose can be formulated in animal models to achieve a circulating plasma concentration range that includes the IC<sub>50</sub> (i.e., the concentration of the test compound that achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma can be measured, for example, by high performance liquid chromatography.

Another example of determination of effective dose for an individual is the ability to directly assay levels of "free" and "bound" compound in the serum of the test subject. Such assays can utilize antibody mimics and/or "biosensors" that have been created

through molecular imprinting techniques. The compound which is able to modulate 13245 activity is used as a template, or "imprinting molecule," to spatially organize polymerizable monomers prior to their polymerization with catalytic reagents. The subsequent removal of the imprinted molecule leaves a polymer matrix that contains a repeated "negative image" of the compound and is able to selectively rebind the molecule under biological assay conditions. Detailed reviews of this technique appear in the art (Ansell et al., 1996, Curr. Opin. Biotechnol. 7:89-94; Shea, 1994, Trends Polymer Sci. 2:166-173). Such "imprinted" affinity matrixes are amenable to ligand-binding assays, whereby the immobilized monoclonal antibody component is replaced by an appropriately imprinted matrix (e.g., a matrix described in Vlatakis et al., 1993, Nature 361:645-647. Through the use of isotope-labeling, the "free" concentration of compound which modulates the expression or activity of 13245 can be readily monitored and used in calculations of IC<sub>50</sub>.

Such "imprinted" affinity matrixes can also be designed to include fluorescent groups whose photon-emitting properties measurably change upon local and selective binding of target compound. These changes can be readily assayed in real time using appropriate fiber optic devices, in turn allowing the dose in a test subject to be quickly optimized based on its individual IC<sub>50</sub>. A rudimentary example of such a "biosensor" is discussed in Kriz et al. (1995, Anal. Chem. 67:2142-2144).

Another aspect of the invention pertains to methods of modulating 13245 expression or activity for therapeutic purposes. Accordingly, in an exemplary embodiment, the modulatory method of the invention involves contacting a cell with a 13245 or agent that modulates one or more of the activities of 13245 protein activity associated with the cell. An agent that modulates 13245 protein activity can be an agent as described herein, such as a nucleic acid or a protein, a naturally-occurring target molecule of a 13245 protein (e.g., a 13245 substrate or receptor), a 13245 antibody, a 13245 agonist or antagonist, a peptidomimetic of a 13245 agonist or antagonist, or other small molecule.

In one embodiment, the agent stimulates one or 13245 activities. Examples of such stimulatory agents include active 13245 protein and a nucleic acid molecule encoding 13245. In another embodiment, the agent inhibits one or more 13245 activities. Examples of such inhibitory agents include antisense 13245 nucleic acid molecules, anti-13245 antibodies, and 13245 inhibitors. These modulatory methods can be performed in vitro (e.g., by culturing the cell with the agent) or, alternatively, in vivo (e.g., by administering the agent to a subject).

As such, the present invention provides methods of treating an individual afflicted with a disease or disorder characterized by aberrant or unwanted expression or activity of a 13245 protein or nucleic acid molecule. In one embodiment, the method involves administering an agent (e.g., an agent identified by a screening assay described herein), or combination of agents that modulates (e.g., up-regulates or down-regulates) 13245 expression or activity. In another embodiment, the method involves administering a 13245 protein or nucleic acid molecule as therapy to compensate for reduced, aberrant, or unwanted 13245 expression or activity.

Stimulation of 13245 activity is desirable in situations in which 13245 is abnormally down-regulated and/or in which increased 13245 activity is likely to have a beneficial effect. For example, stimulation of 13245 activity is desirable in situations in which a 13245 is down-regulated and/or in which increased 13245 activity is likely to have a beneficial effect. Likewise, inhibition of 13245 activity is desirable in situations in which 13245 is abnormally up-regulated and/or in which decreased 13245 activity is likely to have a beneficial effect.

#### Pharmacogenomics

The 13245 molecules of the present invention, as well as agents, or modulators which have a stimulatory or inhibitory effect on 13245 activity (e.g., 13245 gene expression) as identified by a screening assay described herein can be administered to individuals to treat (prophylactically or therapeutically) 13245-associated disorders associated with aberrant or unwanted 13245 activity (e.g., disorders associated with tumorigenesis or induction of an inappropriate immune response). In conjunction with such treatment, pharmacogenomics (i.e., the study of the relationship between an individual's genotype and that individual's response to a foreign compound or drug) can be considered. Differences in metabolism of therapeutics can lead to severe toxicity or therapeutic failure by altering the relation between dose and blood concentration of the pharmacologically active drug. Thus, a physician or clinician can consider applying knowledge obtained in relevant pharmacogenomics studies in determining whether to administer a 13245 molecule or 13245 modulator as well as tailoring the dosage and/or therapeutic regimen of treatment with a 13245 molecule or 13245 modulator.

Pharmacogenomics deals with clinically significant hereditary variations in the response to drugs due to altered drug disposition and abnormal action in affected persons (e.g., Eichelbaum et al., 1996, Clin. Exp. Pharmacol. Physiol. 23:983-985; Linder et al., 1997, Clin. Chem. 43:254-266). In general, two types of pharmacogenetic conditions can be differentiated. Genetic conditions transmitted as a single factor altering the way drugs act on the body (altered drug action) or genetic conditions transmitted as single factors altering the way the body acts on drugs (altered drug metabolism). These pharmacogenetic conditions can occur either as rare genetic defects or as naturally-occurring polymorphisms. For example, glucose-6-phosphate dehydrogenase deficiency (G6PD) is a common inherited enzymopathy in which the main clinical complication is hemolysis after ingestion of oxidant drugs (anti-malarials, sulfonamides, analgesics, nitrofurans) and consumption of fava beans.

One pharmacogenomics approach to identifying genes that predict drug response, known as "a genome-wide association," relies primarily on a high-resolution map of the human genome consisting of already known gene-related markers (e.g., a "bi-allelic" gene marker map which consists of 60,000-100,000 polymorphic or variable sites on the human genome, each of which has two variants). Such a high-resolution genetic map can be compared to a map of the genome of each of a statistically significant number of patients taking part in a Phase II/III drug trial to identify markers associated with a particular observed drug response or side effect. Alternatively, such a high-resolution map can be generated from a combination of some ten million known single nucleotide polymorphisms (SNPs) in the human genome. As used herein, a "SNP" is a common alteration that occurs in a single nucleotide base in a stretch of DNA. For example, a SNP may occur once per every 1000 bases of DNA. A SNP can be involved in a disease process, however, the vast majority may not be disease-associated. Given a genetic map based on the occurrence of such SNPs, individuals can be grouped into genetic categories depending on a particular pattern of SNPs in their individual genome. In such a manner, treatment regimens can be tailored to groups of genetically similar individuals, taking into account traits that can be common among such genetically similar individuals.

Alternatively, a method termed the "candidate gene approach" can be utilized to identify genes that predict drug response. According to this method, if a gene that encodes a drug's target is known (e.g., a 13245 protein of the present invention), all common variants

of that gene can be fairly easily identified in the population and it can be determined if having one version of the gene versus another is associated with a particular drug response.

Alternatively, a method termed "gene expression profiling," can be utilized to identify genes that predict drug response. For example, the gene expression of an animal  
5 dosed with a drug (e.g., a 13245 molecule or 13245 modulator of the present invention) can give an indication whether gene pathways related to toxicity have been turned on.

Information generated from more than one of the above pharmacogenomics approaches can be used to determine appropriate dosage and treatment regimens for prophylactic or therapeutic treatment of an individual. This knowledge, when applied to  
10 dosing or drug selection, can avoid adverse reactions or therapeutic failure and thus enhance therapeutic or prophylactic efficiency when treating a subject with a 13245 molecule or 13245 modulator, such as a modulator identified by one of the exemplary screening assays described herein.

The present invention further provides methods for identifying new agents, or  
15 combinations, that are based on identifying agents that modulate the activity of one or more of the gene products encoded by one or more of the 13245 genes of the present invention, wherein these products can be associated with resistance of the cells to a therapeutic agent. Specifically, the activity of the proteins encoded by the 13245 genes of the present invention can be used as a basis for identifying agents for overcoming agent resistance. By blocking the  
20 activity of one or more of the resistance proteins, target cells, e.g., cells of the immune system, will become sensitive to treatment with an agent that the unmodified target cells were resistant to.

Monitoring the influence of agents (e.g., drugs) on the expression or activity of a 13245 protein can be applied in clinical trials. For example, the effectiveness of an agent  
25 determined by a screening assay as described herein to increase 13245 gene expression, protein levels, or up-regulate 13245 activity, can be monitored in clinical trials of subjects exhibiting decreased 13245 gene expression, protein levels, or down-regulated 13245 activity. Alternatively, the effectiveness of an agent determined by a screening assay to decrease 13245 gene expression, protein levels, or down-regulate 13245 activity, can be monitored in  
30 clinical trials of subjects exhibiting increased 13245 gene expression, protein levels, or up-regulated 13245 activity. In such clinical trials, the expression or activity of a 13245 gene,

and preferably, other genes that have been implicated in, for example, a 13245-associated disorder can be used as a "read out" or markers of the phenotype of a particular cell.

#### Other Embodiments

5 In another aspect, the invention features, a method of analyzing a plurality of capture probes. The method can be used, e.g., to analyze gene expression. The method includes: providing a two-dimensional array having a plurality of addresses, each address of the plurality being positionally distinguishable from each other address of the plurality, and each address of the plurality having a unique capture probe, e.g., a nucleic acid or peptide  
10 sequence; contacting the array with a 13245, preferably purified, nucleic acid, preferably purified, polypeptide, preferably purified, or antibody, and thereby evaluating the plurality of capture probes. Binding, e.g., in the case of a nucleic acid, hybridization with a capture probe at an address of the plurality, is detected, e.g., by signal generated from a label attached to the 13245 nucleic acid, polypeptide, or antibody.

15 The capture probes can be a set of nucleic acids from a selected sample, e.g., a sample of nucleic acids derived from a control or non-stimulated tissue or cell.

The method can include contacting the 13245 nucleic acid, polypeptide, or antibody with a first array having a plurality of capture probes and a second array having a different plurality of capture probes. The results of hybridization can be compared, e.g., to  
20 analyze differences in expression between a first and second sample. The first plurality of capture probes can be from a control sample, e.g., a wild-type, normal, or non-diseased, non-stimulated, sample, e.g., a biological fluid, tissue, or cell sample. The second plurality of capture probes can be from an experimental sample, e.g., a mutant type, at risk, disease-state or disorder-state, or stimulated, sample, e.g., a biological fluid, tissue, or cell sample.

25 The plurality of capture probes can be a plurality of nucleic acid probes each of which specifically hybridizes, with an allele of 13245. Such methods can be used to diagnose a subject, e.g., to evaluate risk for a disease or disorder, to evaluate suitability of a selected treatment for a subject, to evaluate whether a subject has a disease or disorder. 13245 is associated with protein phosphorylation, thus it is useful for evaluating disorders relating to  
30 aberrant protein phosphorylation, such as tumorigenesis and inappropriate cell signaling.

The method can be used to detect SNPs, as described above.

In another aspect, the invention features, a method of analyzing a plurality of probes. The method is useful, e.g., for analyzing gene expression. The method includes: providing a two dimensional array having a plurality of addresses, each address of the plurality being positionally distinguishable from each other address of the plurality having a unique capture probe, e.g., wherein the capture probes are from a cell or subject which express 13245 or from a cell or subject in which a 13245 mediated response has been elicited, e.g., by contact of the cell with 13245 nucleic acid or protein, or administration to the cell or subject 13245 nucleic acid or protein; contacting the array with one or more inquiry probe, wherein an inquiry probe can be a nucleic acid, polypeptide, or antibody (which is preferably other than 13245 nucleic acid, polypeptide, or antibody); providing a two-dimensional array having a plurality of addresses, each address of the plurality being positionally distinguishable from each other address of the plurality, and each address of the plurality having a unique capture probe, e.g., wherein the capture probes are from a cell or subject which does not express 13245 (or does not express as highly as in the case of the 13245 positive plurality of capture probes) or from a cell or subject which in which a 13245 mediated response has not been elicited (or has been elicited to a lesser extent than in the first sample); contacting the array with one or more inquiry probes (which is preferably other than a 13245 nucleic acid, polypeptide, or antibody), and thereby evaluating the plurality of capture probes. Binding, e.g., in the case of a nucleic acid, hybridization with a capture probe at an address of the plurality, is detected, e.g., by signal generated from a label attached to the nucleic acid, polypeptide, or antibody.

In another aspect, the invention features, a method of analyzing a plurality of probes or a sample. The method is useful, e.g., for analyzing gene expression. The method includes: providing a two dimensional array having a plurality of addresses, each address of the plurality being positionally distinguishable from each other address of the plurality having a unique capture probe, contacting the array with a first sample from a cell or subject which express or mal express 13245 or from a cell or subject in which a 13245-mediated response has been elicited, e.g., by contact of the cell with 13245 nucleic acid or protein, or administration to the cell or subject 13245 nucleic acid or protein; providing a two dimensional array having a plurality of addresses, each address of the plurality being positionally distinguishable from each other address of the plurality, and each address of the plurality having a unique capture probe, and contacting the array with a second sample from a

cell or subject which does not express 13245 (or does not express as highly as in the case of the 13245 positive plurality of capture probes) or from a cell or subject which in which a 13245 mediated response has not been elicited (or has been elicited to a lesser extent than in the first sample); and comparing the binding of the first sample with the binding of the second sample. Binding, e.g., in the case of a nucleic acid, hybridization with a capture probe at an address of the plurality, is detected, e.g., by signal generated from a label attached to the nucleic acid, polypeptide, or antibody. The same array can be used for both samples or different arrays can be used. If different arrays are used the plurality of addresses with capture probes should be present on both arrays.

In another aspect, the invention features a method of analyzing 13245, e.g., analyzing structure, function, or relatedness to other nucleic acid or amino acid sequences. The method includes: providing a 13245 nucleic acid or amino acid sequence, e.g., nucleotide sequence from 13245 or a portion thereof; comparing the 13245 sequence with one or more preferably a plurality of sequences from a collection of sequences, e.g., a nucleic acid or protein sequence database; to thereby analyze 13245.

The method can include evaluating the sequence identity between a 13245 sequence and a database sequence. The method can be performed by accessing the database at a second site, e.g., via the internet.

In another aspect, the invention features, a set of oligonucleotides, useful, e.g., for identifying SNPs, or identifying specific alleles of 13245. The set includes a plurality of oligonucleotides, each of which has a different nucleotide at an interrogation position, e.g., an SNP or the site of a mutation. In a preferred embodiment, the plurality of oligonucleotides are identical in sequence with one another (except for differences in length). The oligonucleotides can be provided with differential labels, such that an oligonucleotide that hybridizes to one allele provides a signal that is distinguishable from an oligonucleotide that hybridizes to a second allele.

The sequence of a 13245 molecules is provided in a variety of mediums to facilitate use thereof. A sequence can be provided as a manufacture, other than an isolated nucleic acid or amino acid molecule, which contains a 13245. Such a manufacture can provide a nucleotide or amino acid sequence, e.g., an open reading frame, in a form which allows examination of the manufacture using means not directly applicable to examining the

nucleotide or amino acid sequences, or a subset thereof, as they exists in nature or in purified form.

A 13245 nucleotide or amino acid sequence can be recorded on computer readable media. As used herein, "computer readable media" refers to any medium that can be read and accessed directly by a computer. Such media include, but are not limited to: magnetic storage media, such as floppy discs, hard disc storage medium, and magnetic tape; optical storage media such as CD-ROM; electrical storage media such as RAM and ROM; and hybrids of these categories such as magnetic/optical storage media.

A variety of data storage structures are available to a skilled artisan for creating a computer readable medium having recorded thereon a nucleotide or amino acid sequence of the present invention. The choice of the data storage structure will generally be based on the means chosen to access the stored information. In addition, a variety of data processor programs and formats can be used to store the nucleotide sequence information of the present invention on computer readable medium. The sequence information can be represented in a word processing text file, formatted in commercially-available software such as WordPerfect™ and Microsoft Word™, or represented in the form of an ASCII file, stored in a database application, such as DB2, Sybase™, Oracle™, or the like. The skilled artisan can readily adapt any number of data processor structuring formats (e.g., text file or database) in order to obtain computer readable medium having recorded thereon the nucleotide sequence information of the present invention.

By providing the nucleotide or amino acid sequences of the invention in computer readable form, the skilled artisan can routinely access the sequence information for a variety of purposes. For example, one skilled in the art can use the nucleotide or amino acid sequences of the invention in computer readable form to compare a target sequence or target structural motif with the sequence information stored within the data storage means. A search is used to identify fragments or regions of the sequences of the invention that match a particular target sequence or target motif.

As used herein, a "target sequence" can be any DNA or amino acid sequence of six or more nucleotides or two or more amino acids. A skilled artisan can readily recognize that the longer a target sequence is, the less likely a target sequence will be present as a random occurrence in the database. Typical sequence lengths of a target sequence are from about 10 to 100 amino acids or from about 30 to 300 nucleotide residues. However, it is

well recognized that commercially important fragments, such as sequence fragments involved in gene expression and protein processing, can be of shorter length.

Computer software is publicly available which allows a skilled artisan to access sequence information provided in a computer readable medium for analysis and comparison to other sequences. A variety of known algorithms are disclosed publicly and a variety of commercially available software for conducting search means are and can be used in the computer-based systems of the present invention. Examples of such software include, but are not limited to, MacPattern (EMBL), BLASTN and BLASTX (NCBIA).

Thus, the invention features a method of making a computer readable record of a sequence of a 13245 sequence that includes recording the sequence on a computer readable matrix. In a preferred embodiment, the record includes one or more of the following: identification of an open reading frame; identification of a domain, region, or site; identification of the start of transcription; identification of the transcription terminator; the full length amino acid sequence of the protein, or a mature form thereof; the 5'- end of the translated region; or 5'- and/or 3'-regulatory regions.

In another aspect, the invention features, a method of analyzing a sequence. The method includes: providing a 13245 sequence or record, in computer readable form; comparing a second sequence to the gene name sequence; thereby analyzing a sequence. Comparison can include comparing to sequences for sequence identity or determining if one sequence is included within the other, e.g., determining if the 13245 sequence includes a sequence being compared. In a preferred embodiment, the 13245 or second sequence is stored on a first computer, e.g., at a first site and the comparison is performed, read, or recorded on a second computer, e.g., at a second site. E.g., the 13245 or second sequence can be stored in a public or proprietary database in one computer, and the results of the comparison performed, read, or recorded on a second computer. In a preferred embodiment the record includes one or more of the following: identification of an ORF; identification of a domain, region, or site; identification of the start of transcription; identification of the transcription terminator; the full length amino acid sequence of the protein, or a mature form thereof; the 5'-end of the translated region; or 5'- and/or 3'-regulatory regions.

This invention is further illustrated by the following examples that should not be construed as limiting. The contents of all references, patents and published patent applications cited throughout this application are incorporated herein by reference.

## EXAMPLES

## Example 1

## Identification and Characterization of

## Human 13245 cDNA

The human 13245 nucleotide sequence (Figure 1; SEQ ID NO: 1), which is approximately 6575 nucleotides in length including non-translated regions, contains a predicted methionine-initiated coding sequence at about nucleotide residues 19-6178. The coding sequence encodes a 2053 amino acid protein (SEQ ID NO: 2).

## Example 2

## Tissue Distribution of 13245 mRNA

Northern blot hybridizations with various RNA samples can be performed under standard conditions and washed under stringent conditions, i.e., 0.2×SSC at 65°C. A DNA probe corresponding to all or a portion of the 13245 cDNA (SEQ ID NO: 1) can be used. The DNA can, for example, be radioactively labeled with <sup>32</sup>P-dCTP using the Prime-It™ Kit (Stratagene, La Jolla, CA) according to the instructions of the supplier. Filters containing mRNA from mouse hematopoietic and endocrine tissues, and cancer cell lines (Clontech, Palo Alto, CA) can be probed in ExpressHyb™ hybridization solution (Clontech) and washed at high stringency according to manufacturer's recommendations.

## Example 3

## Recombinant Expression of 13245

## in Bacterial Cells

In this example, 13245 is expressed as a recombinant glutathione-S-transferase (GST)-fusion polypeptide in E. coli and the fusion polypeptide is isolated and characterized. Specifically, 13245 nucleic acid sequences are fused to GST nucleic acid sequences and this fusion construct is expressed in E. coli, e.g., strain PEB199. Expression of the GST-13245 fusion construct in PEB199 is induced with IPTG. The recombinant fusion polypeptide is purified from crude bacterial lysates of the induced PEB199 strain by affinity chromatography on glutathione beads. Using polyacrylamide gel electrophoretic analysis of the polypeptide

purified from the bacterial lysates, the molecular weight of the resultant fusion polypeptide is determined.

#### Example 4

##### Expression of Recombinant 13245 Protein in COS Cells

To express the 13245 gene in COS cells, the pcDNA/Amp vector by Invitrogen Corporation (San Diego, CA) is used. This vector contains an SV40 origin of replication, an ampicillin resistance gene, an E. coli replication origin, a CMV promoter followed by a polylinker region, and an SV40 intron and polyadenylation site. A DNA fragment encoding the entire 13245 protein and an HA tag (Wilson et al., 1984, Cell 37:767) or a FLAG® tag fused in-frame to its 3'-end of the fragment is cloned into the polylinker region of the vector, thereby placing the expression of the recombinant protein under the control of the CMV promoter.

To construct the plasmid, the 13245 DNA sequence is amplified by PCR using two primers. The 5' primer contains the restriction site of interest followed by approximately twenty nucleotides of the 13245 coding sequence starting from the initiation codon; the 3'-end sequence contains complementary sequences to the other restriction site of interest, a translation stop codon, the HA tag or FLAG® tag and the last 20 nucleotides of the 13245 coding sequence. The PCR amplified fragment and the pcDNA/Amp vector are digested with the appropriate restriction enzymes and the vector is dephosphorylated using the CIAP enzyme (New England Biolabs, Beverly, MA). Preferably the two restriction sites chosen are different so that the 13245 gene is inserted in the desired orientation. The ligation mixture is transformed into E. coli cells (strains HB101, DH5alpha, SURE, available from Stratagene Cloning Systems, La Jolla, CA, can be used), the transformed culture is plated on ampicillin media plates, and resistant colonies are selected. Plasmid DNA is isolated from transformants and examined by restriction analysis for the presence of the correct fragment.

COS cells are subsequently transfected with the 13245-pcDNA/Amp plasmid DNA using the calcium phosphate or calcium chloride co-precipitation methods, DEAE-dextran-mediated transfection, lipofection, or electroporation. Other suitable methods for transfecting host cells can be found in Sambrook et al., (1989, Molecular Cloning: A Laboratory Manual. 2nd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY).

The expression of the 13245 polypeptide is detected by radiolabeling (<sup>35</sup>S-methionine or <sup>35</sup>S-cysteine, available from NEN, Boston, MA, can be used) and immunoprecipitation (Harlow et al., 1988, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY) using an HA-specific monoclonal antibody. Briefly, the cells are labeled  
5 for 8 hours with <sup>35</sup>S-methionine (or <sup>35</sup>S-cysteine). The culture media are then collected and the cells are lysed using detergents (RIPA buffer, 150 millimolar NaCl, 1% NP-40, 0.1% SDS, 0.5% DOC, 50 millimolar Tris, pH 7.5). Both the cell lysate and the culture media are precipitated with an HA-specific monoclonal antibody. Precipitated polypeptides are then analyzed by SDS-PAGE.

10 Alternatively, DNA containing the 13245 coding sequence is cloned directly into the polylinker of the pcDNA/Amp vector using the appropriate restriction sites. The resulting plasmid is transfected into COS cells in the manner described above, and the expression of the 13245 polypeptide is detected by radiolabeling and immunoprecipitation using a 13245-specific monoclonal antibody.

#### 15 Equivalents

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

## CLAIMS

What is claimed is:

1. An isolated nucleic acid molecule selected from the group consisting of:
  - a) a nucleic acid molecule comprising a nucleotide sequence which is at least 60% identical to the nucleotide sequence of either of SEQ ID NOs: 1 and 3;
  - b) a nucleic acid molecule comprising a fragment of at least 300 nucleotides of the nucleotide sequence of either of SEQ ID NOs: 1 and 3;
  - c) a nucleic acid molecule which encodes a polypeptide comprising the amino acid sequence of SEQ ID NO: 2;
  - d) a nucleic acid molecule which encodes a fragment of a polypeptide comprising the amino acid sequence of SEQ ID NO: 2, wherein the fragment comprises at least 15 contiguous amino acids of SEQ ID NO: 2; and
  - e) a nucleic acid molecule which encodes a naturally-occurring allelic variant of a polypeptide comprising the amino acid sequence of SEQ ID NO: 2, wherein the nucleic acid molecule hybridizes with a nucleic acid molecule comprising one of SEQ ID NO: 1, SEQ ID NO: 3, and a complement thereof, under stringent conditions.
2. The isolated nucleic acid molecule of claim 1, which is selected from the group consisting of:
  - a) a nucleic acid comprising the nucleotide sequence of either of SEQ ID NOs: 1 and 3; and
  - b) a nucleic acid molecule which encodes a polypeptide comprising the amino acid sequence of SEQ ID NO: 2.
3. The nucleic acid molecule of claim 1 further comprising a vector nucleic acid sequence.
4. The nucleic acid molecule of claim 1 further comprising a nucleic acid sequence encoding a heterologous polypeptide.
5. A host cell that contains the nucleic acid molecule of claim 1.
6. The host cell of claim 5, wherein the host cell is a mammalian host cell.
7. A non-human mammalian host cell containing the nucleic acid molecule of claim 1.
8. An isolated polypeptide selected from the group consisting of:

a) a polypeptide which is encoded by a nucleic acid molecule comprising a nucleotide sequence which is at least 60% identical to a nucleic acid comprising the nucleotide sequence of either of SEQ ID NOs: 1 and 3, and a complement of one of these;

b) a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of SEQ ID NO: 2, wherein the polypeptide is encoded by a nucleic acid molecule which hybridizes with a nucleic acid molecule comprising one of SEQ ID NO: 1, SEQ ID NO: 3, and a complement of either of these under stringent conditions; and

c) a fragment of a polypeptide comprising the amino acid sequence of SEQ ID NO: 2, wherein the fragment comprises at least 15 contiguous amino acids of SEQ ID NO: 2.

9. The isolated polypeptide of claim 8 comprising the amino acid sequence of SEQ ID NO: 2.

10. The polypeptide of claim 8, further comprising a heterologous amino acid sequence.

11. An antibody that selectively binds with a polypeptide of claim 8.

12. A method for producing a polypeptide selected from the group consisting of:

a) a polypeptide comprising the amino acid sequence of SEQ ID NO: 2;

b) a polypeptide comprising a fragment of the amino acid sequence of SEQ ID NO: 2, wherein the fragment comprises at least 15 contiguous amino acids of SEQ ID NO: 2; and

c) a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of SEQ ID NO: 2, wherein the polypeptide is encoded by a nucleic acid molecule which hybridizes with a nucleic acid molecule comprising one of SEQ ID NO: 1, SEQ ID NO: 3, and a complement of either of these, under stringent conditions;

the method comprising culturing the host cell of claim 5 under conditions in which the nucleic acid molecule is expressed.

13. A method for detecting the presence of a polypeptide of claim 8 in a sample, comprising:

a) contacting the sample with a compound which selectively binds with a polypeptide of claim 8; and

b) determining whether the compound binds with the polypeptide in the sample.

14. The method of claim 13, wherein the compound that binds with the polypeptide is an antibody.

15. A kit comprising a compound that selectively binds with a polypeptide of claim 8 and instructions for use.

16. A method for detecting the presence of a nucleic acid molecule of claim 1 in a sample, comprising the steps of:

- a) contacting the sample with a nucleic acid probe or primer which selectively hybridizes with the nucleic acid molecule; and
- b) determining whether the nucleic acid probe or primer binds with a nucleic acid molecule in the sample.

17. The method of claim 16, wherein the sample comprises mRNA molecules and is contacted with a nucleic acid probe.

18. A kit comprising a compound that selectively hybridizes with a nucleic acid molecule of claim 1 and instructions for use.

19. A method for identifying a compound which binds with a polypeptide of claim 8 comprising the steps of:

- a) contacting a polypeptide, or a cell expressing a polypeptide of claim 8 with a test compound; and
- b) determining whether the polypeptide binds with the test compound.

20. The method of claim 19, wherein the binding of the test compound with the polypeptide is detected by a method selected from the group consisting of:

- a) detection of binding by direct detecting of test compound/polypeptide binding;
- b) detection of binding using a competition binding assay; and
- c) detection of binding using an assay for 13245-mediated signal transduction.

21. A method for modulating the activity of a polypeptide of claim 8 comprising contacting a polypeptide or a cell expressing a polypeptide of claim 8 with a compound which binds with the polypeptide in a sufficient concentration to modulate the activity of the polypeptide.

22. A method for identifying a compound which modulates the activity of a polypeptide of claim 8, comprising:

- a) contacting a polypeptide of claim 8 with a test compound; and
- b) determining the effect of the test compound on the activity of the polypeptide to thereby identify a compound which modulates the activity of the polypeptide.

23. Use of a modulator of the activity of 13245 protein for making a medicament for modulating the ability of a cell to catalyze interconversion of the phosphorylated and de-phosphorylated forms a GTPase protein.

24. Use according to claim 23, wherein the modulator is an inhibitor of 13245 gene expression.

25. Use according to claim 24, wherein the inhibitor is an antisense oligonucleotide which hybridizes under stringent conditions with a transcript of the 13245 gene.

26. Use according to claim 25, wherein the antisense oligonucleotide comprises at least 15 nucleotide residues.

27. Use according to claim 25, wherein the transcript is an mRNA.

28. Use according to claim 24, wherein the inhibitor is an antisense oligonucleotide which hybridizes under stringent conditions with a polynucleotide having the nucleotide sequence SEQ ID NO: 1.

29. Use according to claim 24, wherein the inhibitor is an antisense oligonucleotide which hybridizes under stringent conditions with a polynucleotide having the nucleotide sequence SEQ ID NO: 3.

30. Use according to claim 23, wherein the modulator does not significantly affect 13245 gene expression in the cell.

31. Use according to claim 23, wherein the modulator is an agent which inhibits an activity of 69087 protein.

32. Use according to claim 31, wherein the agent is an antibody which specifically binds with 69087 protein.

34. A method for assessing whether a test compound is useful for modulating at least one phenomenon selected from the group consisting of (1) interconversion of the phosphorylated and de-phosphorylated forms of a serine, threonine, or tyrosine residue of a GTPase protein; (2) cell contractility; (3) cell growth; (4) cell conductivity; (5) entry of a cell into the cell cycle; (6) progression of a cell through the cell cycle; (7) mitogenesis; (8) cell metabolism; (9) gene transcription; (11) cytokinesis; (12) cell shape; (13) cell movement; (14) integration of a viral genome into a host cell genome; (15) maintenance of a viral genome within a host cell genome; (16) a cytological change in a virus-infected host cell; (17) virus production in a virus-infected host cell; (18) interaction of a virion with a membrane of

a virus-infected host cell; and (19) encapsulation of a virion within a portion of a membrane of a virus-infected host cell, the method comprising:

a) adding the test compound to a first composition comprising a polypeptide that has an amino acid sequence at least 90% identical to SEQ ID NO: 2 and that exhibits a 13245 activity; and

b) comparing the 13245 activity in the first composition and in a second composition that is substantially identical to the first composition except that it does not comprise the test compound,

whereby a difference in the 13245 activity in the first and second compositions is an indication that the test compound is useful for modulating the phenomenon.

35. The method of claim 34, wherein the activity is GTPase kinase activity.

36. The method of claim 34, wherein the protein has the amino acid sequence SEQ ID NO: 2.

37. The method of claim 34, wherein the composition comprises a cell comprising a nucleic acid encoding the protein.

38. The method of claim 37, wherein the nucleic acid is the genome of the cell.

39. The method of claim 37, wherein the nucleic acid comprises the 13245 gene.

40. A method for assessing whether a test compound is useful for modulating at least one phenomenon selected from the group consisting of (1) interconversion of the phosphorylated and de-phosphorylated forms of a serine, threonine, or tyrosine residue of a GTPase protein; (2) cell contractility; (3) cell growth; (4) cell conductivity; (5) entry of a cell into the cell cycle; (6) progression of a cell through the cell cycle; (7) mitogenesis; (8) cell metabolism; (9) gene transcription; (11) cytokinesis; (12) cell shape; (13) cell movement; (14) integration of a viral genome into a host cell genome; (15) maintenance of a viral genome within a host cell genome; (16) a cytological change in a virus-infected host cell; (17) virus production in a virus-infected host cell; (18) interaction of a virion with a membrane of a virus-infected host cell; and (19) encapsulation of a virion within a portion of a membrane of a virus-infected host cell, the method comprising:

a) adding the test compound to a first composition comprising a cell which comprises a nucleic acid that encodes a polypeptide that has an amino acid sequence at least 90% identical to SEQ ID NO: 2 and that exhibits a 13245 activity; and

b) comparing 13245 activity in the first composition and in a second composition that is substantially identical to the first composition except that it does not comprise the test compound,

whereby a difference in the 13245 activity in the first and second compositions is an indication that the test compound is useful for modulating the phenomenon.

41. A method of making a pharmaceutical composition for modulating at least one phenomenon selected from the group consisting of (1) interconversion of the phosphorylated and de-phosphorylated forms of a serine, threonine, or tyrosine residue of a GTPase protein; (2) cell contractility; (3) cell growth; (4) cell conductivity; (5) entry of a cell into the cell cycle; (6) progression of a cell through the cell cycle; (7) mitogenesis; (8) cell metabolism; (9) gene transcription; (11) cytokinesis; (12) cell shape; (13) cell movement; (14) integration of a viral genome into a host cell genome; (15) maintenance of a viral genome within a host cell genome; (16) a cytological change in a virus-infected host cell; (17) virus production in a virus-infected host cell; (18) interaction of a virion with a membrane of a virus-infected host cell; and (19) encapsulation of a virion within a portion of a membrane of a virus-infected host cell, the method comprising:

a) selecting a test compound useful for modulating the phenomenon according to the method of claim 34; and

b) combining the test compound with a pharmaceutically acceptable carrier in order to make the pharmaceutical composition.

42. A method of modulating, in a human, at least one phenomenon selected from the group consisting of (1) interconversion of the phosphorylated and de-phosphorylated forms of a serine, threonine, or tyrosine residue of a GTPase protein; (2) cell contractility; (3) cell growth; (4) cell conductivity; (5) entry of a cell into the cell cycle; (6) progression of a cell through the cell cycle; (7) mitogenesis; (8) cell metabolism; (9) gene transcription; (11) cytokinesis; (12) cell shape; (13) cell movement; (14) integration of a viral genome into a host cell genome; (15) maintenance of a viral genome within a host cell genome; (16) a cytological change in a virus-infected host cell; (17) virus production in a virus-infected host cell; (18) interaction of a virion with a membrane of a virus-infected host cell; and (19) encapsulation of

a virion within a portion of a membrane of a virus-infected host cell, the method comprising administering the pharmaceutical composition of claim 41 to the human in an amount effective to modulate the phenomenon.

43. A method for identifying a compound useful for modulating at least one phenomenon selected from the group consisting of (1) interconversion of the phosphorylated and de-phosphorylated forms of a serine, threonine, or tyrosine residue of a GTPase protein; (2) cell contractility; (3) cell growth; (4) cell conductivity; (5) entry of a cell into the cell cycle; (6) progression of a cell through the cell cycle; (7) mitogenesis; (8) cell metabolism; (9) gene transcription; (11) cytokinesis; (12) cell shape; (13) cell movement; (14) integration of a viral genome into a host cell genome; (15) maintenance of a viral genome within a host cell genome; (16) a cytological change in a virus-infected host cell; (17) virus production in a virus-infected host cell; (18) interaction of a virion with a membrane of a virus-infected host cell; and (19) encapsulation of a virion within a portion of a membrane of a virus-infected host cell, the method comprising:

a) contacting the test compound and a polypeptide selected from the group consisting of

i) a polypeptide which is encoded by a nucleic acid molecule comprising a portion having a nucleotide sequence which is at least 90% identical to one of SEQ ID NOs: 1 and 3; and

ii) a fragment of a polypeptide having either an amino acid sequence comprising SEQ ID NO: 2, wherein the fragment comprises at least 25 contiguous amino acid residues of SEQ ID NO: 2

or a cell that expresses the polypeptide; and

b) determining whether the polypeptide binds with the test compound, whereby binding of the polypeptide and the test compound is an indication that the test compound is useful for modulating the phenomenon.

44. The method of claim 43, wherein the polypeptide exhibits an epitope in common with a polypeptide having the amino acid sequence SEQ ID NO: 2.

M	L	K	F	K	Y	G	A	R	N	P	L	D	A	G	15	
AGAGCCGCCAGTGGGAG	ATG	TTG	AAG	TTC	AAA	TAT	GGA	GCG	AAT	CCT	TTG	GAT	GCT	GGT	45	
A	A	E	P	I	A	S	R	L	N	L	F	Q	G	K	P	35
GCT	GCT	GAA	CCC	ATT	GCC	AGC	CGG	TCC	AGG	CTG	AAT	CTG	TTC	TTC	CAG	105
P	F	M	T	Q	Q	Q	M	S	P	L	S	R	E	G	I	55
CCC	TTT	ATG	ACT	CAA	CAG	CAG	ATG	TCT	CCT	CTT	TCC	CGA	GAA	GGG	ATA	165
F	V	L	F	E	C	S	Q	S	P	A	L	M	K	I	K	75
TTT	GTT	CTC	TTT	GAA	GAA	TGC	AGT	CAG	CCT	GCT	CTG	ATG	AAG	ATT	AAG	225
F	V	R	K	Y	S	D	T	I	A	E	L	Q	E	L	Q	95
TTT	GTC	CGG	AAG	TAT	TCC	GAC	ACC	ATA	GCT	GAG	TTA	CAG	GAG	CTC	CAG	285
D	F	E	V	R	S	L	V	G	C	G	H	F	A	E	V	115
GAC	TTC	GAA	GTC	AGA	AGT	CTT	GTA	GGT	TGT	GGT	CAC	TTT	GCT	GAA	GTG	345
E	K	A	T	G	D	I	Y	A	M	K	V	M	K	K	A	135
GAG	AAA	GCA	ACC	GGG	GAC	ATC	TAT	GCT	ATG	AAA	GTG	ATG	AAG	AAG	GCT	405
Q	E	Q	V	S	F	E	E	E	R	N	I	L	S	R	S	155
CAG	GAG	CAG	GTT	TCA	TTT	TTT	GAG	GAA	GAG	CGG	AAC	ATA	TTA	TCT	CGA	465

Fig. 1A

W	I	P	Q	L	Q	L	Q	Y	A	F	Q	D	K	N	H	L	Y	L	M	E	E		175
	TGG	ATC	CCC	CAA	TTA	CAG	TAT	GCC	TTT	CAG	GAC	AAA	AAT	CAC	CTT	TAT	TAT	CTG	ATG	GAG	GAA		525
Y	Q	P	G	G	D	L	L	S	L	L	L	N	R	Y	E	D	Q	L	D	E		195	
	TAT	CAG	CCT	GGA	GGG	GAC	TTG	CTG	TCA	CTT	TTG	AAT	AGA	TAT	GAG	GAC	CAG	TTA	GAT	GAA		585	
N	L	I	Q	F	Y	L	A	E	L	L	I	L	A	V	H	S	V	H	L	M		215	
	AAC	CTG	ATA	CAG	TTT	TAC	CTA	GCT	GAG	CTG	ATT	TTG	GCT	GTT	CAC	AGC	GTT	CAT	CTG	ATG		645	
G	Y	V	H	R	D	I	K	P	E	N	I	L	V	D	R	T	G	H	I		235		
	GGA	TAC	GTG	CAT	CGA	GAC	ATC	AAG	CCT	GAG	AAC	ATT	CTC	GTT	GAC	CGC	ACA	GGA	CAC	ATC		705	
K	L	V	D	F	G	S	A	A	K	M	N	S	N	K	M	V	N	A	K		255		
	AAG	CTG	GTG	GAT	TTT	GGA	TCT	GCC	GCG	AAA	ATG	AAT	TCA	AAC	AAG	ATG	GTG	AAT	GCC	AAA		765	
L	P	I	G	T	P	D	Y	M	A	P	E	V	L	T	V	M	N	G	D		275		
	CTC	CCG	ATT	GGG	ACC	CCA	GAT	TAC	ATG	GCT	CCT	GAA	GTG	CTG	ACT	GTG	ATG	AAC	GGG	GAT		825	
G	K	G	T	Y	G	L	D	C	D	W	W	S	V	G	V	I	A	Y	E		295		
	GGA	AAA	GGC	ACC	TAC	GGC	CTG	GAC	TGT	GAC	TGG	TGG	TCA	GTG	GGC	GTG	ATT	GCC	TAT	GAG		885	
M	I	Y	G	R	S	P	F	A	E	G	T	S	A	R	T	F	N	N	I		315		
	ATG	ATT	TAT	GGG	AGA	TCC	CCC	TTC	GCA	GAG	GGA	ACC	TCT	GCC	AGA	ACC	TTC	AAT	AAC	ATT		945	

Fig. 1B

M	N	F	Q	R	F	L	K	F	P	D	D	P	K	V	S	S	D	F	L		335
ATG	AAT	TTC	CAG	CGG	TTT	TTG	AAA	TTT	CCA	GAT	GAC	CCC	AAA	GTG	AGC	AGT	GAC	TTT	CTT		1005
D	L	I	Q	S	L	L	C	G	Q	K	E	R	L	K	F	E	G	L	C		355
GAT	CTG	ATT	CAA	AGC	TTG	TTG	TGC	GGC	CAG	AAA	GAG	AGA	CTG	AAG	TTT	GAA	GGT	CTT	TGC		1065
C	H	P	F	F	S	K	I	D	W	N	N	I	R	N	S	P	P	P	F		375
TGC	CAT	CCT	TTC	TTC	TCT	AAA	ATT	GAC	TGG	AAC	AAC	ATT	CGT	AAC	TCT	CCT	CCC	CCC	TTC		1125
V	P	T	L	K	S	D	D	D	T	S	N	F	D	E	P	E	K	N	S		395
GTT	CCC	ACC	CTC	AAG	TCT	GAC	GAT	GAC	ACC	TCC	AAT	TTT	GAT	GAA	CCA	GAG	AAG	AAT	TCG		1185
W	V	S	S	S	P	C	Q	L	S	P	S	G	F	S	G	E	E	L	P		415
TGG	GTT	TCA	TCC	TCT	CCG	TGC	CAG	CTG	AGC	CCC	TCA	GGC	TTC	TCG	GGT	GAA	GAA	CTG	CCG		1245
F	V	G	F	S	Y	S	K	A	L	G	I	L	G	R	S	E	S	V	V		435
TTT	GTG	GGG	TTT	TCG	TAC	AGC	AAG	GCA	CTG	GGG	ATT	CTT	GGT	AGA	TCT	GAG	TCT	GTT	GTG		1305
S	G	L	D	S	P	A	K	T	S	S	M	E	K	K	L	L	I	K	S		455
TCG	GGT	CTG	GAC	TCC	CCT	GCC	AAG	ACT	AGC	TCC	ATG	GAA	AAG	AAA	CTT	CTC	ATC	AAA	AGC		1365
K	E	L	Q	D	S	Q	D	K	C	H	K	M	E	Q	E	M	T	R	L		475
AAA	GAG	CTA	CAA	GAC	TCT	CAG	GAC	AAG	TGT	CAC	AAG	ATG	GAG	CAG	GAA	ATG	ACC	CGG	TTA		1425

Fig. 1C

H R R V S E V E A V L S Q K E V E L K A	495
CAT CGG AGA GTG TCA GAG GTG GAG GCT GTG CTT AGT CAG AAG GAG GTG GAG CTG AAG GCC	1485
S E T Q R S L L E Q D L A T Y I T E C S	515
TCT GAG ACT CAG AGA TCC CTC CTG GAG CAG GAC CTT GCT ACC TAC ATC ACA GAA TGC AGT	1545
S L K R S L E E Q A R M E V S Q E D D K A	535
AGC TTA AAG CGA AGT TTG GAG CAA GCA CGG ATG GAG GTG TCC CAG GAG GAT GAC AAA GCA	1605
L Q L L H D I R E Q S R K L Q E I K E Q	555
CTG CAG CTT CTC CAT GAT ATC AGA GAG CAG AGC CGG AAG CTC CAA GAA ATC AAA GAG CAG	1665
E Y Q A Q V E E M R L M M N Q L E E D L	575
GAG TAC CAG GCT CAA GTG GAA GAA ATG AGG TTG ATG ATG AAT CAG TTG GAA GAG GAT CTT	1725
V S A R R R S D L Y E S E L R E S R L A	595
GTC TCA GCA AGA AGA CGG AGT GAT CTC TAC TAC GAA TCT GAG CTG AGA GAG TCT CGG CTT GCT	1785
A E E F K R K A T E C Q H K L L K A K D	615
GCT GAA GAA TTC AAG CGG AAA GCG ACA GAA TGT CAG CAT AAA CTG TTG AAG GCT AAG GAT	1845
Q G K P E V G E Y A K L E K I N A E Q Q	635
CAA GGG AAG CCT GAA GTG GGA GAA TAT GCG AAA CTG GAG AAG ATC AAT GCT GAG CAG CAG	1905

Fig. 1D

L K I Q E L E K L E K A A K E R A E R	655
CTC AAA ATT CAG GAG CTC CAA GAG AAA CTG GAG AAG GCT GCA AAG GAG CGA GCC GAG AGG	1965
E L E K L Q N R E D S S E G I R K K L V	675
GAG CTG GAG AAG CTG CAG AAC CGA GAG GAT TCT TCT GAA GGC ATC AGA AAG AAG CTG GTG	2025
E A E E R R H S L E N K V K R L E T M E	695
GAA GCT GAG GAA CGC CGC CAT TCT CTG GAG AAC AAG GTA AAG AGA CTA GAG ACC ATG GAG	2085
R R E N R L K D I Q T K S Q Q I Q Q M	715
CGT AGA GAA AAC AGA CTG AAG GAT GAC ATC CAG ACA AAA TCC CAA CAG ATC CAG CAG ATG	2145
A D K I L E L E E K H R E A Q V S A Q H	735
GCT GAT AAA ATT CTG GAG CTC GAA GAG AAA CAT CGG GAG GCC CAA GTC TCA GCC CAG CAC	2205
L E V H L K Q K E Q H Y E E K I K V L D	755
CTA GAA GTG CAC CTG AAA CAG AAA GAG CAG CAC TAT GAG GAA AAG ATT AAA GTG TTG GAC	2265
N Q I K K D L A D K E T L E N M M Q R H	775
AAT CAG ATA AAG AAA GAC CTG GCT GAT GAG AAC ACA CTG GAG AAC ATG ATG CAG AGA CAC	2325
E E E A H E K G K I L S E Q K A M I N A	795
GAG GAG GAG GCC CAT GAG AAG GGC AAA ATT CTC AGC GAA CAG AAG GCG ATG ATC AAT GCT	2385

Fig. 1E

M	D	S	K	I	R	S	L	E	Q	R	I	V	E	L	S	E	A	N	K	815
ATG	GAT	TCC	AAG	ATC	AGA	TCC	CTG	GAA	CAG	AGG	ATT	GTG	GAA	CTG	TCT	GAA	GCC	AAT	AAA	2445
L	A	A	N	S	S	L	F	T	Q	R	N	M	K	A	Q	E	E	M	I	835
CTT	GCA	GCA	AAT	AGC	AGT	CTT	TTT	ACC	CAA	AGG	AAC	ATG	AAG	GCC	CAA	GAA	GAG	ATG	ATT	2505
S	E	L	R	Q	Q	K	F	Y	L	E	T	Q	A	G	K	L	E	A	Q	855
TCT	GAA	CTC	AGG	CAA	CAG	AAA	TTT	TAC	CTG	GAG	ACA	CAG	GCT	GGG	AAG	TTG	GAG	GCC	CAG	2565
N	R	K	L	E	E	Q	L	E	K	I	S	H	Q	D	H	S	D	K	N	875
AAC	CGA	AAA	CTG	GAG	GAG	CAG	CTG	GAG	AAG	ATC	AGC	CAC	CAA	GAC	CAC	AGT	GAC	AAG	AAT	2625
R	L	L	E	L	E	T	R	L	R	E	V	S	L	E	H	E	E	Q	K	895
CGG	CTG	CTG	GAA	CTG	GAG	ACA	AGA	TTG	CGG	GAG	GTC	AGT	CTA	GAG	CAC	GAG	GAG	CAG	AAA	2685
L	E	L	K	R	Q	L	T	E	L	Q	L	S	L	Q	E	R	E	S	Q	915
CTG	GAG	CTC	AAG	CGC	CAG	CTC	ACA	GAG	CTA	CAG	CTC	TCC	CTG	CAG	GAG	CGC	GAG	TCA	CAG	2745
L	T	A	L	Q	A	A	R	A	A	L	E	S	Q	L	R	Q	A	K	T	935
TTG	ACA	GCC	CTG	CAG	GCT	GCA	CGG	GCG	GCC	CTG	GAG	AGC	CAG	CTT	CGC	CAG	GCG	AAG	ACA	2805
E	L	E	E	T	T	A	E	A	E	E	E	I	Q	A	L	T	A	H	R	955
GAG	CTG	GAA	GAG	ACC	ACA	GCA	GAA	GCT	GAA	GAG	GAG	ATC	CAG	GCA	CTC	ACG	GCA	CAT	AGA	2865

Fig. 1F

D E I Q R K F D A L R N S C T V I T D L 975  
 GAT GAA ATC CAG CGC AAA TTT GAT GCT CTT CGT AAC AGC TGT ACT GTA ATC ACA GAC CTG 2925  
  
 E E Q L N Q L T E D N A E L N N Q N F Y 995  
 GAG GAG CAG CTA AAC CAG CTG ACC GAG GAC AAC GCT GAA CTC AAC AAC CAA AAC TTC TAC 2985  
  
 L S K Q L D E A S G A N D E I V Q L R S 1015  
 TTG TCC AAA CAA CTC GAT GAG GCT TCT GGC GCC AAC GAC GAG ATT GTA CAA CTG CGA AGT 3045  
  
 E V D H L R R E I T E R E M Q L T S Q K 1035  
 GAA GTG GAC CAT CTC CGC CGG GAG ATC ACG GAA CGA CGA GAG ATG CAG CTT ACC AGC CAG AAG 3105  
  
 Q T M E A L K T T C T M L E E Q V M D L 1055  
 CAA ACG ATG GAG GCT CTG AAG ACC ACG TGC ACC ATG CTG GAG GAA CAG GTC ATG GAT TTG 3165  
  
 E A L N D E L L E K E R Q W E A W R S V 1075  
 GAG GCC CTA AAC GAT GAG CTG CTA GAA AAA GAG CGG CAG TGG GAG GCC TGG AGG AGC GTC 3225  
  
 L G D E K S Q F E C R V R E L Q R M L D 1095  
 CTG GGT GAT GAG AAA TCC CAG TTT GAG TGT CGG GTT CGA GAG CTG CAG AGA ATG CTG GAC 3285  
  
 T E K Q S R A R A D Q R I T E S R Q V 1115  
 ACC GAG AAA CAG AGC AGG GCG AGA GCC GAT CAG CGG ATC ACC GAG TCT CGC CAG GTG GTG 3345

Fig. 1G

E	L	A	V	K	E	H	K	A	E	I	L	A	L	A	Q	Q	A	L	K	E	1135
GAG	CTG	GCA	GTG	AAG	GAG	CAC	AAG	GCT	GAG	ATT	CTC	GCT	CTG	CTG	CAG	CAG	GCT	CTC	AAA	GAG	3405
Q	K	L	K	A	E	S	L	S	D	K	L	N	D	L	E	K	K	K	H	A	1155
CAG	AAG	CTG	AAG	GCC	GAG	AGC	CTC	TCT	GAC	AAG	CTC	AAT	GAC	CTG	GAG	AAG	AAG	CAT	GCT	3465	
M	L	E	M	N	A	R	S	L	Q	Q	K	L	E	T	E	R	E	L	K	1175	
ATG	CTT	GAA	ATG	AAT	GCC	CGA	AGC	TTA	CAG	CAG	AAG	CTG	GAG	ACT	GAA	CGA	GAG	CTC	AAA	3525	
Q	R	L	L	E	E	Q	A	K	L	Q	Q	Q	M	D	L	Q	K	N	H	1195	
CAG	AGG	CTT	CTG	GAA	GAG	CAA	GCC	AAA	TTA	CAG	CAG	CAG	ATG	GAC	CTG	CAG	AAA	AAT	CAC	3585	
I	F	R	L	T	Q	G	L	Q	E	A	L	D	R	A	D	L	L	K	T	1215	
ATT	TTC	CGT	CTG	ACT	CAA	GGA	CTG	CAA	GAA	GCT	CTA	GAT	CGG	GCT	GAT	CTA	CTG	AAG	ACA	3645	
E	R	S	D	L	E	Y	Q	L	E	N	I	Q	V	L	Y	S	H	E	K	1235	
GAA	AGA	AGT	GAC	TTG	GAG	TAT	CAG	CTG	GAA	AAC	ATT	CAG	GTT	CTC	TAT	TCT	CAT	GAA	AAG	3705	
V	K	M	E	G	T	I	S	Q	Q	T	K	L	I	D	F	L	Q	A	K	1255	
GTG	AAA	ATG	GAA	GGC	ACT	ATT	TCT	CAA	CAA	ACC	AAA	CTC	ATT	GAT	TTT	CTG	CAA	GCC	AAA	3765	
M	D	Q	P	A	K	K	K	K	G	L	F	S	R	R	K	E	D	P	A	1275	
ATG	GAC	CAA	CCT	GCT	AAA	AAG	AAA	AAG	GGT	TTA	TTT	AGT	CGA	CGG	AAA	GAG	GAC	CCT	GCT	3825	

Fig. 1H

L	P	T	Q	V	P	L	Q	Y	N	E	L	K	L	A	L	E	K	E	K		1295
TTA	CCC	ACA	CAG	GTT	CCT	CTG	CAG	TAC	AAT	GAG	CTG	AAG	CTG	GCC	CTG	GAG	AAG	GAG	AAA		3885
A	R	C	A	E	L	E	E	A	L	Q	K	T	R	I	E	L	R	S	A		1315
GCT	CGC	TGT	GCA	GAG	CTA	GAG	GAA	GCC	CTT	CAG	AAG	ACC	CGC	ATC	GAG	CTC	CGG	TCC	GCC		3945
R	E	E	A	A	H	R	K	A	T	D	H	P	H	P	S	T	P	A	T		1335
CGG	GAG	GAA	GCT	GCC	CAC	CGC	AAA	GCA	ACG	GAC	CAC	CCA	CAC	CCA	TCC	ACG	CCA	GCC	ACC		4005
A	R	Q	Q	I	A	M	S	A	I	V	R	S	P	E	H	Q	P	S	A		1355
GCG	AGG	CAG	CAG	ATC	GCC	ATG	TCC	GCC	ATC	GTG	CGG	TCG	CCA	GAG	CAC	CAG	CCC	AGT	GCC		4065
M	S	L	L	A	P	P	S	S	R	R	K	E	S	S	T	P	E	E	F		1375
ATG	AGC	CTG	CTG	GCC	CCG	CCA	TCC	AGC	CGC	AGA	AAG	GAG	TCT	TCA	ACT	CCA	GAG	GAA	TTT		4125
S	R	R	L	K	E	R	M	H	H	N	I	P	H	R	F	N	V	G	L		1395
AGT	CGG	CGT	CTT	AAG	GAA	CGC	ATG	CAC	CAC	AAT	ATT	CCT	CAC	CGA	TTC	AAC	GTA	GGA	CTG		4185
N	M	R	A	T	K	C	A	V	C	L	D	T	V	H	F	G	R	Q	A		1415
AAC	ATG	CGA	GCC	ACA	AAG	TGT	GCT	GTG	TGT	CTG	GAT	ACC	GTG	CAC	TTT	GGA	CGC	CAG	GCA		4245
S	K	C	L	E	C	Q	V	M	C	H	P	K	C	S	T	C	L	P	A		1435
TCC	AAA	TGT	CTC	GAA	TGT	CAG	GTG	ATG	TGT	CAC	CCC	AAG	TGC	TCC	ACG	TGC	TTG	CCA	GCC		4305

Fig. 11

T	C	G	L	P	A	E	Y	A	T	H	F	T	E	A	F	C	R	D	K	1455
ACC	TGC	GGC	TTG	CCT	GCT	GAA	TAT	GCC	ACA	CAC	TTC	ACC	GAG	GCC	TTC	TGC	CGT	GAC	AAA	4365
M	N	S	P	G	L	Q	T	K	E	P	S	S	S	L	H	L	E	G	W	1475
ATG	AAC	TCC	CCA	GGT	CTC	CAG	ACC	AAG	GAG	CCC	AGC	AGC	AGC	TTG	CAC	CTG	GAA	GGG	TGG	4425
M	K	V	P	R	N	N	K	R	G	Q	Q	G	W	D	R	K	Y	I	V	1495
ATG	AAG	GTG	CCC	AGG	AAT	AAC	AAA	CGA	GGA	CAG	CAA	GGC	TGG	GAC	AGG	AAG	TAC	ATT	GTC	4485
L	E	G	S	K	V	L	I	Y	D	N	E	A	R	E	A	G	Q	R	P	1515
CTG	GAG	GGA	TCA	AAA	GTC	CTC	ATT	TAT	GAC	AAT	GAA	GCC	AGA	GAA	GCT	GGA	CAG	AGG	CCG	4545
V	E	E	F	E	L	C	L	P	D	G	D	V	S	I	H	G	A	V	G	1535
GTG	GAA	GAA	TTT	GAG	CTG	TGC	CTT	CCC	GAC	GGG	GAT	GTA	TCT	ATT	CAT	GGT	GCC	GTT	GGT	4605
A	S	E	L	A	N	T	A	K	A	E	K	A	E	A	D	A	K	L	L	1555
GCT	TCC	GAA	CTC	GCA	AAT	ACA	GCC	AAA	GCA	GAA	AAA	GCA	GAA	GCT	GAT	GCT	AAA	CTG	CTT	4665
G	N	S	L	L	K	L	E	G	D	D	R	L	D	M	N	C	T	L	P	1575
GGA	AAC	TCC	CTG	CTG	AAA	CTG	GAA	GGT	GAT	GAC	CGT	CTA	GAC	ATG	AAC	TGC	ACG	CTG	CCC	4725
F	S	D	Q	V	V	L	V	G	T	E	E	G	L	Y	A	L	N	V	L	1595
TTC	AGT	GAC	CAG	GTG	GTG	TTG	GTG	GGC	ACC	GAG	GAA	GGG	CTC	TAC	GCC	CTG	AAT	GTC	TTG	4785

Fig. 1J

K N S L T H V P G I G A V F Q I Y I I K	1615
AAA AAC TCC CTA ACC CAT GTC CCA GGA ATT GGA GCA GTC TTC CAA ATT TAT ATT ATC AAG	4845
D L E K L L M I A G E E R A L C L V D V	1635
GAC CTG GAG AAG CTA CTC ATG ATA GCA GGA GAA GAG CGG GCA CTG TGT CTT GTG GAC GTG	4905
K K V K Q S L A Q S H L P A Q P D I S P	1655
AAG AAA GTG AAA CAG TCC CTG GCC CAG TCC CAC CTG CCT GGC CAG CCC GAC ATC TCA CCC	4965
N I F E A V K G C H L F G A G G C AAG ATT GAG AAC GGG	1675
AAC ATT TTT GAA GCT GTC AAG GGC TGC CAC TTG TTT GGG GCA GGC AAG ATT GAG AAC GGG	5025
L C I C A A M P S K V V I L R Y N E N L	1695
CTC TGC ATC TGT GCA GCC ATG CCC AGC AAA GTC GTC ATT CTC CGC TAC AAC GAA AAC CTC	5085
S K Y C I R K E I E T S E P C S C I H F	1715
AGC AAA TAC TGC ATC CGG AAA GAG ATA GAG ACC TCA GAG CCC TGC AGC TGT ATC CAC TTC	5145
T N Y S I L I G T N K F Y E I D M K Q Y	1735
ACC AAT TAC AGT ATC CTC ATT GGA ACC ACC AAA TTC TAC GAA ATC GAC ATG AAG CAG TAC	5205
T L E E F L L D K N D H S L A P A V F A A	1755
ACG CTC GAG GAA TTC CTG GAT AAG AAT GAC CAT TCC TTG GCA CCT GCT GTG TTT GCC GCC	5265

Fig. 1K

S	S	N	S	F	P	V	S	I	V	Q	V	N	S	A	G	Q	R	E	E	1775
TCT	TCC	AAC	AGC	TTC	CCT	GTC	TCA	ATC	GTG	CAG	GTG	AAC	AGC	GCA	GGG	CAG	CGA	GAG	GAG	5325
Y	L	L	C	F	H	E	F	G	V	F	V	D	S	Y	G	R	R	S	R	1795
TAC	TTG	CTG	TGT	TTC	CAC	GAA	TTT	GGA	GTG	TTC	GTG	GAT	TCT	TAC	GGA	AGA	CGT	AGC	CGC	5385
T	D	D	L	K	W	S	R	L	P	L	A	F	A	Y	R	E	P	Y	L	1815
ACA	GAC	GAT	CTC	AAG	TGG	AGT	CGC	TTA	CCT	TTG	GCC	TTT	GCC	TAC	AGA	GAA	CCC	TAT	CTG	5445
F	V	T	H	F	N	S	L	E	V	I	E	I	Q	A	R	S	S	A	G	1835
TTT	GTG	ACC	CAC	TTC	AAC	TCA	CTC	GAA	GTA	ATT	GAG	ATC	CAG	GCA	CGC	TCC	TCA	GCA	GGG	5505
T	P	A	R	A	Y	L	D	I	P	N	P	R	Y	L	G	P	A	I	S	1855
ACC	CCT	GCC	CGA	GCG	TAC	CTG	GAC	ATC	CCG	AAC	CCG	CGC	TAC	CTG	GGC	CCT	GCC	ATT	TCC	5565
S	G	A	I	Y	L	A	S	S	Y	Q	D	K	L	R	V	I	C	C	K	1875
TCA	GGA	GCG	ATT	TAC	TTG	GCG	TCC	TCA	TAC	CAG	GAT	AAA	TTA	AGG	GTC	ATT	TGC	TGC	AAG	5625
G	N	L	V	K	E	S	G	T	E	H	H	R	G	P	S	T	S	R	S	1895
GGA	AAC	CTC	GTG	AAG	GAG	TCC	GGC	ACT	GAA	CAC	CAC	CGG	GGC	CCG	TCC	ACC	TCC	CGC	AGC	5685
S	P	N	K	R	G	P	P	T	Y	N	E	H	I	T	K	R	V	A	S	1915
AGC	CCC	AAC	AAG	CGA	GGC	CCA	CCC	ACG	TAC	AAC	GAG	CAC	ATC	ACC	AAG	CGC	GTG	GCC	TCC	5745

Fig. 1L

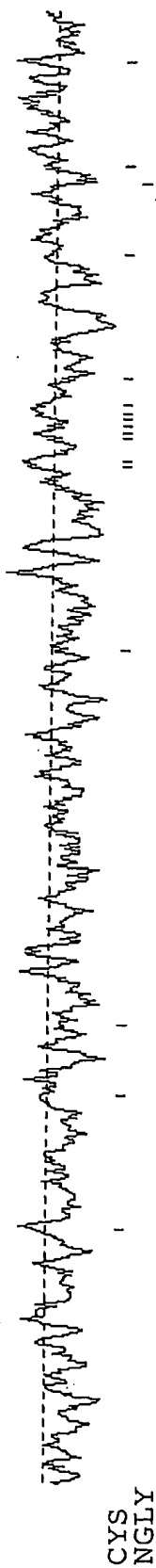
S	P	A	P	P	E	G	P	S	H	P	R	E	P	S	T	P	H	R	Y	1935
AGC	CCA	GCG	CCG	CCC	GAA	GGC	CCC	AGC	CAC	CCG	CGA	GAG	CCA	AGC	ACA	CCC	CAC	CGC	TAC	5805
R	E	G	R	T	E	L	R	R	D	K	S	P	G	R	P	L	E	R	E	1955
CGC	GAG	GGG	CGG	ACC	GAG	CTG	CGC	AGG	GAC	AAG	TCT	CCT	GGC	CGC	CCC	CTG	GAG	CGA	GAG	5865
K	S	P	G	R	M	L	S	T	R	R	E	R	S	P	G	R	L	F	E	1975
AAG	TCC	CCC	GGC	CGG	ATG	CTC	AGC	ACG	CGG	AGA	GAG	CGG	TCC	CCC	GGG	AGG	CTG	TTT	GAA	5925
D	S	S	R	G	R	L	P	A	G	A	V	R	T	P	L	S	Q	V	N	1995
GAC	AGC	AGC	AGG	GGC	CGG	CTG	CCT	GCG	GGA	GCC	GTG	AGG	ACC	CCG	CTG	TCC	CAG	GTG	AAC	5985
K	G	R	G	Q	S	A	S	Q	V	F	T	V	N	T	V	T	Y	Y	D	20153
AAG	GGA	AGA	GGG	CAG	AGT	GCC	TCT	CAA	GTT	TTC	ACG	GTT	AAC	ACT	GTC	ACC	TAT	TAT	GAC	604525
W	N	K	K	L	D	N	L	P	A	N	W	S	V	L	R	I	I	Q	L	2035
TGG	AAT	AAA	AAG	CTG	GAC	AAC	CTG	CCA	GCT	AAC	TGG	TCA	GTC	CTG	AGG	ATC	ATC	CAG	CTG	6105
N	G	E	I	R	Q	Q	V	E	K	S	V	L	R	T	D	Y	C	*		2053
AAT	GGA	GAA	ATC	CGG	CAG	CAG	GTT	GAA	AAG	TCT	GTT	CTG	AGA	ACA	GAT	TAT	TGC	TGA		6162
GCAGAGTT	CATGTGACTT	CTAGACGTG	GTGACTT	AAAAAATGGCCTT	AAGGCTGCAGAGCCAGCCACCTCTGCTTACAA	AAAGAGTACTT	AGTGCACATGACTGT	AAAGAAACAATTGTAAACCTCATCTAGAAATCAGAAAGCTTCTAATTCTATA	GAAATGACACCTCCCTGGAGCCGAGAGACAATCTGTTGTTGATTTTGAAGGACAGGCAAGACCACTGTATTAGTT	CCATAGCCAGGCTCAACAGGACAGTGGCTGGCCTTAAACACACAGATGACTGGAATGATGTGTGCTCAGTC	CCTGTTCCAGAAATTTACTGGCAAGGAGTTAGCATTCATTTTGGCTTAAGAAAAATCGAGAAATGTAGGTTTAGA									

Fig. 1M

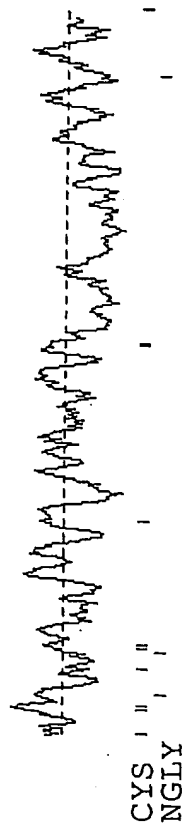
14/25



1 41 81 121 161 201 241 281 321 361 401 441 481 521 561 601 641 681 721 761 801



841 881 921 961 1001 1041 1081 1121 1161 1201 1241 1281 1321 1361 1401 1441 1481 1521 1561 1601 1641



1681 1721 1761 1801 1841 1881 1921 1961 2001 2041

Fig. 2

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Fig. 3A

1	13245	MLKFKYGARN	PLDAGAAEPI	ASRASRLNLF	FQKPPFMTQ	QQMSPLSREG	50
	AAC72823	MLKFKYGVN	PPEASASEPI	ASRASRLNLF	FQKPPPLMTQ	QQMSALSREG	
	AAC27933	.....	.....	.....	.....	.....	
	P49025	.....	.....	.....	.....	.....	
	O14578	.....	.....	.....	.....	.....	
51	13245	ILDALFVLFE	ECSQPALMKI	KHVSNEVRKY	SDTIAELQEL	QPSAKDFEVR	100
	AAC72823	MLDALFALFE	ECSQPALMKM	KHVSSFVQKY	SDTIAELREL	QPSARDFEVR	
	AAC27933	.....	.....	.....	.....	.....	
	P49025	.....	.....	.....	.....	.....	
	O14578	.....	.....	.....	.....	.....	
101	13245	SLVGCCHFAE	VQVREKATG	DIYAMKVMKK	KALLAQEQVS	FFEEERNILS	150
	AAC72823	SLVGCCHFAE	VQVREKATG	DVYAMKIMKK	KALLAQEQVS	FFEEERNILS	
	AAC27933	.....	.....	.....	.....	.....	
	P49025	.....	.....	.....	.....	.....	
	O14578	.....	.....	.....	.....	.....	
151	13245	RSTSPWIPQL	QYAFQDKNHL	YLMEEYQPGG	DLLSLLNRYE	DQLDENLIQF	200
	AAC72823	RSTSPWIPQL	QYAFQDKNNL	YLVMEYQPGG	DFLSLLNRYE	DQLDSEMIQF	
	AAC27933	.....	.....	.....	.....	.....	
	P49025	.....	.....	.....	.....	.....	
	O14578	.....	.....	.....	.....	.....	

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Fig. 3B

13245	YLAELILAVH	SVHLMGYVHR	DIKPENILVD	RTGHIKLVDF	GSAAKMNSNK	250
AAC72823	YLAELILAVH	SVHOMGYVHR	DIKPENILID	RTGEIKLVDF	GSAAKMNSNK	
AAC27933	.....	.....	.....	.....	.....	
P49025	.....	.....	.....	.....	.....	
O14578	.....	.....	.....	.....	.....	
201						
13245	MVNAKLPIGT	PDYMAPEVLT	VMNGDGKGT	GLDCDWWSVG	VIAAYEMIYGR	300
AAC72823	.VDAKLPIGT	PDYMAPEVLT	VMNEDRRGT	GLDCDWWSVG	VVAYEMVYGR	
AAC27933	.....	.....	.....	.....	.....	
P49025	.....	.....	.....	.....	.....	
O14578	.....	.....	.....	.....	.....	
251						
13245	SPFAEGTSAR	TENNIMNFQR	FLKFPDDPKV	SSDFLDLIQS	LLCGQKERLK	350
AAC72823	TPFTEGTSAR	TENNIMNFQR	FLKFPDDPKV	SSELLDLLQS	LLCVQKERLK	
AAC27933	.....	.....	.....	.....	.....	
P49025	.....	.....	.....	.....	.....	
O14578	.....	.....	.....	.....	.....	
301						
13245	FEGLCCHPEF	SKIDWNNIRN	SPPFVPTLK	SDDDTSNFEDE	PEKNSWVSSS	400
AAC72823	FEGLCCHPEF	ARTDWNIRN	SPPFVPTLK	SDDDTSNFEDE	PEKNSWAFIL	
AAC27933	.....	.....	...FEVPTLK	SDDDTSNFEDE	PEKNSWVSSS	
P49025	.....	.....	.....	.....	.....	
O14578	.....	.....	.....	.....	.....	
351						





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Fig. 3E

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801
13245 ILSEQKAMIN AMDSKIRSLE QRIVELSEAN KLAANSSSLFT QRNMKAQEEM 850
AAC72823 ILSEQKAMIN AMDSKIRSLE QRIVELSEAN KLAANSSSLFT QRNMKAQEEM
AAC27933 ILSEQKAMIN AMDSKIRSLE QRIVELSEAN KLAANSSSLFT QRNMKAQEEM
P49025 ILSEQKAMIN AMDSKIRSLE QRIVELSEAN KLAANSSSLFT QRNMKAQEEM
O14578 ILSEQKAMIN AMDSKIRSLE QRIVELSEAN KLAANSSSLFT QRNMKAQEEM

851
13245 ISELRQKIFY LETQAGKLEA QNRKLEEQLE KISHQDHSDK NRLLLELETRL 900
AAC72823 ISELRQKIFY LETQAGKLEA QNRKLEEQLE KISHQDHSDK SRLLLELETRL
AAC27933 ISELRQKIFY LETQAGKLEA QNRKLEEQLE KISHQDHSDK SRLLLELETRL
P49025 ISELRQKIFY LETQAGKLEA QNRKLEEQLE KISHQDHSDK SRLLLELETRL
O14578 ISELRQKIFY LETQAGKLEA QNRKLEEQLE KISHQDHSDK NRLLLELETRL

901
13245 REVSLHEHEEQ KLELKRQLTE LQLSLQERES QLTALQAARA ALESQLRQAK 950
AAC72823 REVSLHEHEEQ KLELKRQLTE LQLSLQERES QLTALQAARA ALESQLRQAK
AAC27933 REVSLHEHEEQ KLELKRQLTE LQLSLQERES QLTALQAARA ALESQLRQAK
P49025 REVSLHEHEEQ KLELKRQLTE LQLSLQERES QLTALQAARA ALESQLRQAK
O14578 REVSLHEHEEQ KLELKRQLTE LQLSLQERES QLTALQAARA ALESQLRQAK

951
13245 TELEETTAEA EEEIQALTAH RDEIQRKFDA LRNSCTVITD LEEQINQLTE 1000
AAC72823 TELEETTAEA EEEIQALTAH RDEIQRKFDA LRNSCTVITD LEEQINQLTE
AAC27933 TELEETTAEA EEEIQALTAH RDEIQRKFDA LRNSCTVITD LEEQINQLTE
P49025 TELEETTAEA EEEIQALTAH RDEIQRKFDA LRNSCTVITD LEEQINQLTE
O14578 TELEETTAEA EEEIQALTAH RDEIQRKFDA LRNSCTVITD LEEQINQLTE
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Fig. 3F

1001	1050
13245 DNAELNNQNF YLSKQLDEAS GANDEIVQLR SEVDHLRREI TEREMQLTSQ	
AAC72823 DNAELNNQNF YLSKQLDEAS GANDEIVQLR SEVDHLRREI TEREMQLTSQ	
AAC27933 DNAELNNQNF YLSKQLDEAS GANDEIVQLR SEVDHLRREI TEREMQLTSQ	
P49025 DNAELNNQNF YLSKQLDEAS GANDEIVQLR SEVDHLRREI TEREMQLTSQ	
O14578 DNAELNNQNF YLSKQLDEAS GANDEIVQLR SEVDHLRREI TEREMQLTSQ	
1051	1100
13245 KQTMEALKTT CTMLEEQVMD LEALNDELLE KERQWEAWRS VLGDEKSQFE	
AAC72823 KQTMEALKTT CTMLEEQVLD LEALNDELLE KERQWEAWRS VLGDEKSQFE	
AAC27933 KQTMEALKTT CTMLEEQVLD LEALNDELLE KERQWEAWRS VLGDEKSQFE	
P49025 KQTMEALKTT CTMLEEQVLD LEALNDELLE KERQWEAWRS VLGDEKSQFE	
O14578 KQTMEALKTT CTMLEEQVMD LEALNDELLE KERQWEAWRS VLGDEKSQFE	
1101	1150
13245 CRVRELQRL DTEKQSRARA DQRITESRQV VELAVKEHKA EILALQQALK	
AAC72823 CRVRELQRL DTEKQSRARA DQRITESRQV VELAVKEHKA EILALQQALK	
AAC27933 CRVRELQRL DTEKQSRARA DQRITESRQV VELAVKEHKA EILALQQALK	
P49025 CRVRELQRL DTEKQSRARA DQRITESRQV VELAVKEHKA EILALQQALK	
O14578 CRVRELQRL DTEKQSRARA DQRITESRQV VELAVKEHKA EILALQQALK	
1151	1200
13245 EQKLKAESLS DKLNDLEKXH AMLEMNARSL QQKLETEREL KQRLLEEQAK	
AAC72823 EQKLKAESLS DKLNDLEKXH AMLEMNARSL QQKLETEREL KQRLLEEQAK	
AAC27933 EQKLKAESLS DKLNDLEKXH AMLEMNARSL QQKLETEREL KQRLLEEQAK	
P49025 EQKLKAESLS DKLNDLEKXH AMLEMNARSL QQKLETEREL KQRLLEEQAK	
O14578 EQKLKAESLS DKLNDLEKXH AMLEMNARSL QQKLETEREL KQRLLEEQAK	

Fig. 3G

1201	1250				
13245	LOQQMDLQKN	HIFRLTQGLQ	EALDRADLLK	TERSDLEYQL	ENIQVLYSHE
AAC72823	LOQQMDLQKN	HIFRLTQGLQ	EALDRADLLK	TERSDLEYQL	ENIQVLYSHE
AAC27933	LOQQMDLQKN	HIFRLTQGLQ	EALDRADLLK	TERSDLEYQL	ENIQVLYSHE
P49025	LOQQMDLQKN	HIFRLTQGLQ	EALDRADLLK	TERSDLEYQL	ENIQVLYSHE
O14578	LOQQMDLQKN	HIFRLTQGLQ	EALDRADLLK	TERSDLEYQL	ENIQVLYSHE
1251	1300				
13245	KVKMEGTISQ	QTKLIDFLQA	KMDQPAKKKK	GLFSRRKEDP	ALPTQVPLQY
AAC72823	KVKMEGTISQ	QTKLIDFLQA	KMDQPAKKKK	.....	.....VPLQY
AAC27933	KVKMEGTISQ	QTKLIDFLQA	KMDQPAKKKK	.....	.....VPLQY
P49025	KVKMEGTISQ	QTKLIDFLQA	KMDQPAKKKK	.....	.....VPLQY
O14578	KVKMEGTISQ	QTKLIDFLQA	KMDQPAKKKK	.....	.....VPLQY
1301	1350				
13245	NELKLALKE	KARCAELEEA	LQKTRIELRS	AREEAAHRKA	TDHPHPSTPA
AAC72823	NELKLALKE	KARCAELEEA	LQKTRIELRS	AREEAAHRKA	TDHPHPSTPA
AAC27933	NELKLALKE	KARCAELEEA	LQKTRIELRS	AREEAAHRKA	TDHPHPSTPA
P49025	NELKLALKE	KARCAELEEA	LQKTRIELRS	AREEAAHRKA	TDHPHPSTPA
O14578	NELKLALKE	KARCAELEEA	LQKTRIELRS	AREEAAHRKA	TDHPHPSTPA
1351	1400				
13245	TARQQIAMSA	IVRSPEHQPS	AMSLAPPSS	RRKESSTPEE	FSRRLKERMH
AAC72823	TARQQIAMSA	IVRSPEHQPS	AMSLAPPSS	RRKESSTPEE	FSRRLKERMH
AAC27933	TARQQIAMSA	IVRSPEHQPS	AMSLAPPSS	RRKESSTPEE	FSRRLKERMH
P49025	TARQQIAMSA	IVRSPEHQPS	AMSLAPPSS	RRKESSTPEE	FSRRLKERMH
O14578	TARQQIAMSA	IVRSPEHQPS	AMSLAPPSS	RRKESSTPEE	FSRRLKERMH

[illegible]

[illegible]

Fig. 3J

1801	1850
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O14578 YLLEEFDDKN DHSLAPAVFA ASSNSFPVSI VQVNSAGQRE EYLLCFHEFG	
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O14578 VFVDSYGRRS RTDDLLKWSRL PLAFAYREPY LFVTHFNSLE VIEIQARSSA	
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25/25

Fig. 3K

2001	2050
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O14578 YR..EGRTEL RRDKSPGRPL EREKSPGRML STRRERSPGR LFEDSSRGRL	
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## SEQUENCE LISTING

<110> KAPELLER-LIBERMANN, Rosana  
MILLENNIUM PHARMACEUTICALS, INC.

<120> 13245, A Novel Human Myotonic Dystrophy Type Protein  
Kinase and Uses Therefor

<130> 10147-57WO

<140> Not Yet Assigned

<141> 2001-10-23

<150> US 60/242,429

<151> 2000-10-23

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Ser Gln Leu Thr Ala Leu 930	Gln Ala Ala Arg Ala 935	Ala Leu Glu Ser Gln 940
Leu Arg Gln Ala Lys Thr 945	Glu Leu Glu Glu Thr 950	Thr Ala Glu Ala Glu 955 960
Glu Glu Ile Gln Ala Leu 965	Thr Ala His Arg Asp 970	Glu Ile Gln Arg Lys 975
Phe Asp Ala Leu Arg Asn 980	Ser Cys Thr Val Ile 985	Thr Asp Leu Glu Glu 990
Gln Leu Asn Gln Leu Thr 995	Glu Asp Asn Ala Glu 1000	Leu Asn Asn Gln Asn 1005
Phe Tyr Leu Ser Lys Gln 1010	Leu Asp Glu Ala Ser 1015	Gly Ala Asn Asp Glu 1020
Ile Val Gln Leu Arg Ser 1025	Glu Val Asp His Leu 1030	Arg Arg Glu Ile Thr 1035 1040
Glu Arg Glu Met Gln Leu 1045	Thr Ser Gln Lys Gln 1050	Thr Met Glu Ala Leu 1055
Lys Thr Thr Cys Thr Met 1060	Leu Glu Glu Gln Val 1065	Leu Asp Leu Glu Ala 1070
Leu Asn Asp Glu Leu Leu 1075	Glu Lys Glu Arg Gln 1080	Trp Glu Ala Trp Arg 1085
Ser Val Leu Gly Asp Glu 1090	Lys Ser Gln Phe Glu 1095	Cys Arg Val Arg Glu 1100
Leu Gln Arg Met Leu Asp 1105	Thr Glu Lys Gln Ser 1110	Arg Ala Arg Ala Asp 1115 1120
Gln Arg Ile Thr Glu Ser 1125	Arg Gln Val Val Glu 1130	Leu Ala Val Lys Glu 1135
His Lys Ala Glu Ile Leu 1140	Ala Leu Gln Gln Ala 1145	Leu Lys Glu Gln Lys 1150
Leu Lys Ala Glu Ser Leu 1155	Ser Asp Lys Leu Asn 1160	Asp Leu Glu Lys Lys 1165

His Ala Met Leu Glu Met Asn Ala Arg Ser Leu Gln Gln Lys Leu Glu  
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 Thr Glu Arg Glu Leu Lys Gln Arg Leu Leu Glu Glu Gln Ala Lys Leu  
 1185 1190 1195 1200  
 Gln Gln Gln Met Asp Leu Gln Lys Asn His Ile Phe Arg Leu Thr Gln  
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 Gly Leu Gln Glu Ala Leu Asp Arg Ala Asp Leu Leu Lys Thr Glu Arg  
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 Ser Asp Leu Glu Tyr Gln Leu Glu Asn Ile Gln Val Leu Tyr Ser His  
 1235 1240 1245  
 Glu Lys Val Lys Met Glu Gly Thr Ile Ser Gln Gln Thr Lys Leu Ile  
 1250 1255 1260  
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 1265 1270 1275 1280  
 Pro Leu Gln Tyr Asn Glu Leu Lys Leu Ala Leu Glu Lys Glu Lys Ala  
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 Arg Cys Ala Glu Leu Glu Glu Ala Leu Gln Lys Thr Arg Ile Glu Leu  
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 His Pro Ser Thr Pro Ala Thr Ala Arg Gln Gln Ile Ala Met Ser Ala  
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 Pro Pro Ser Ser Arg Arg Lys Glu Ser Ser Thr Pro Glu Glu Phe Ser  
 1365 1370 1375  
 Arg Arg Leu Lys Glu Arg Met His His Asn Ile Pro His Arg Phe Asn  
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 1395 1400 1405  
 Val His Phe Gly Arg Gln Ala Ser Lys Cys Leu Glu Cys Gln Val Met  
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 Cys His Pro Lys Cys Ser Thr Cys Leu Pro Ala Thr Cys Gly Leu Pro  
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 1445 1450 1455  
 Asn Ser Pro Gly Leu Gln Ser Lys Glu Pro Gly Ser Ser Leu His Leu  
 1460 1465 1470  
 Glu Gly Trp Met Lys Val Pro Arg Asn Asn Lys Arg Gly Gln Gln Gly  
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 Trp Asp Arg Lys Tyr Ile Val Leu Glu Gly Ser Lys Val Leu Ile Tyr  
 1490 1495 1500

Asp Asn Glu Ala Arg Glu Ala Gly Gln Arg Pro Val Glu Glu Phe Glu  
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 Leu Cys Leu Pro Asp Gly Asp Val Ser Ile His Gly Ala Val Gly Ala  
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 Ser Glu Leu Ala Asn Thr Ala Lys Ala Asp Val Pro Tyr Ile Leu Lys  
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 Met Glu Ser His Pro His Thr Thr Cys Trp Pro Gly Arg Thr Leu Tyr  
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 Glu Ser Val Val Ala Gly Gly Arg Val Ser Arg Glu Lys Ala Glu Ala  
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 Arg Leu Asp Met Asn Cys Thr Leu Pro Phe Ser Asp Gln Val Val Leu  
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 Val Gly Thr Glu Glu Gly Leu Tyr Ala Leu Asn Val Leu Lys Asn Ser  
 1635 1640 1645  
 Leu Thr His Ile Pro Gly Ile Gly Ala Val Phe Gln Ile Tyr Ile Ile  
 1650 1655 1660  
 Lys Asp Leu Glu Lys Leu Leu Met Ile Ala Gly Glu Glu Arg Ala Leu  
 1665 1670 1675 1680  
 Cys Leu Val Asp Val Lys Lys Val Lys Gln Ser Leu Ala Gln Ser His  
 1685 1690 1695  
 Leu Pro Ala Gln Pro Asp Val Ser Pro Asn Ile Phe Glu Ala Val Lys  
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 Gly Cys His Leu Phe Ala Ala Gly Lys Ile Glu Asn Ser Leu Cys Ile  
 1715 1720 1725  
 Cys Ala Ala Met Pro Ser Lys Val Val Ile Leu Arg Tyr Asn Asp Asn  
 1730 1735 1740  
 Leu Ser Lys Tyr Cys Ile Arg Lys Glu Ile Glu Thr Ser Glu Pro Cys  
 1745 1750 1755 1760  
 Ser Cys Ile His Phe Thr Asn Tyr Ser Ile Leu Ile Gly Thr Asn Lys  
 1765 1770 1775  
 Phe Tyr Glu Ile Asp Met Lys Gln Tyr Thr Leu Asp Glu Phe Leu Asp  
 1780 1785 1790  
 Lys Asn Asp His Ser Leu Ala Pro Ala Val Phe Ala Ser Ser Ser Asn  
 1795 1800 1805  
 Ser Phe Pro Val Ser Ile Val Gln Ala Asn Ser Ala Gly Gln Arg Glu  
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 Glu Tyr Leu Leu Cys Phe His Glu Phe Gly Val Phe Val Asp Ser Tyr

[illegible]

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<212> PRT
<213> Mus musculus
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      20          25          30
Pro Ser Gly Phe Ser Gly Glu Glu Leu Pro Phe Val Gly Phe Ser Tyr
      35          40          45
Ser Lys Ala Leu Gly Tyr Leu Gly Arg Ser Glu Ser Val Val Ser Ser
  50          55          60

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Leu Asp Ser Pro Ala Lys Val Ser Ser Met Glu Lys Lys Leu Leu Ile  
 65 70 75 80  
 Lys Ser Lys Glu Leu Gln Asp Ser Gln Asp Lys Cys His Lys Met Glu  
 85 90 95  
 Gln Glu Met Thr Arg Leu His Arg Arg Val Ser Glu Val Glu Ala Val  
 100 105 110  
 Leu Ser Gln Lys Glu Val Glu Leu Lys Ala Ser Glu Thr Gln Arg Ser  
 115 120 125  
 Leu Leu Glu Gln Asp Leu Ala Thr Tyr Ile Thr Glu Cys Ser Ser Leu  
 130 135 140  
 Lys Arg Ser Leu Glu Gln Ala Arg Met Glu Val Ser Gln Glu Asp Asp  
 145 150 155 160  
 Lys Ala Leu Gln Leu Leu His Asp Ile Arg Glu Gln Ser Arg Lys Leu  
 165 170 175  
 Gln Glu Ile Lys Glu Gln Glu Tyr Gln Ala Gln Val Glu Glu Met Arg  
 180 185 190  
 Leu Met Met Asn Gln Leu Glu Glu Asp Leu Val Ser Ala Arg Arg Arg  
 195 200 205  
 Ser Asp Leu Tyr Glu Ser Glu Leu Arg Glu Ser Arg Leu Ala Ala Glu  
 210 215 220  
 Glu Phe Lys Arg Lys Ala Asn Glu Cys Gln His Lys Leu Met Lys Ala  
 225 230 235 240  
 Lys Asp Gln Gly Lys Pro Glu Val Gly Glu Tyr Ser Lys Leu Glu Lys  
 245 250 255  
 Ile Asn Ala Glu Gln Gln Leu Lys Ile Gln Glu Leu Gln Glu Lys Leu  
 260 265 270  
 Glu Lys Ala Val Lys Ala Ser Thr Glu Ala Thr Glu Leu Leu Gln Asn  
 275 280 285  
 Ile Arg Gln Ala Lys Glu Arg Ala Glu Arg Glu Leu Glu Lys Leu His  
 290 295 300  
 Asn Arg Glu Asp Ser Ser Glu Gly Ile Lys Lys Lys Leu Val Glu Ala  
 305 310 315 320  
 Glu Glu Leu Glu Glu Lys His Arg Glu Ala Gln Val Ser Ala Gln His  
 325 330 335  
 Leu Glu Val His Leu Lys Gln Lys Glu Gln His Tyr Glu Glu Lys Ile  
 340 345 350  
 Lys Val Leu Asp Asn Gln Ile Lys Lys Asp Leu Ala Asp Lys Glu Ser  
 355 360 365  
 Leu Glu Asn Met Met Gln Arg His Glu Glu Glu Ala His Glu Lys Gly  
 370 375 380  
 Lys Ile Leu Ser Glu Gln Lys Ala Met Ile Asn Ala Met Asp Ser Lys

385	390	395	400
Ile Arg Ser Leu Glu Gln Arg Ile Val Glu Leu Ser Glu Ala Asn Lys	405	410	415
Leu Ala Ala Asn Ser Ser Leu Phe Thr Gln Arg Asn Met Lys Ala Gln	420	425	430
Glu Glu Met Ile Ser Glu Leu Arg Gln Gln Lys Phe Tyr Leu Glu Thr	435	440	445
Gln Ala Gly Lys Leu Glu Ala Gln Asn Arg Lys Leu Glu Glu Gln Leu	450	455	460
Glu Lys Ile Ser His Gln Asp His Ser Asp Lys Ser Arg Leu Leu Glu	465	470	475
Leu Glu Thr Arg Leu Arg Glu Val Ser Leu Glu His Glu Glu Gln Lys	485	490	495
Leu Glu Leu Lys Arg Gln Leu Thr Glu Leu Gln Leu Ser Leu Gln Glu	500	505	510
Arg Glu Ser Gln Leu Thr Ala Leu Gln Ala Ala Arg Ala Ala Leu Glu	515	520	525
Ser Gln Leu Arg Gln Ala Lys Thr Glu Leu Glu Glu Thr Thr Ala Glu	530	535	540
Ala Glu Glu Glu Ile Gln Ala Leu Thr Ala His Arg Asp Glu Ile Gln	545	550	555
Arg Lys Phe Asp Ala Leu Arg Asn Ser Cys Thr Val Ile Thr Asp Leu	565	570	575
Glu Glu Gln Leu Asn Gln Leu Thr Glu Asp Asn Ala Glu Leu Asn Asn	580	585	590
Gln Asn Phe Tyr Leu Ser Lys Gln Leu Asp Glu Ala Ser Gly Ala Asn	595	600	605
Asp Glu Ile Val Gln Leu Arg Ser Glu Val Asp His Leu Arg Arg Glu	610	615	620
Ile Thr Glu Arg Glu Met Gln Leu Thr Ser Gln Lys Gln Thr Met Glu	625	630	635
Ala Leu Lys Thr Thr Cys Thr Met Leu Glu Glu Gln Val Leu Asp Leu	645	650	655
Glu Ala Leu Asn Asp Glu Leu Leu Glu Lys Glu Arg Gln Trp Glu Ala	660	665	670
Trp Arg Ser Val Leu Gly Asp Glu Lys Ser Gln Phe Glu Cys Arg Val	675	680	685
Arg Glu Leu Gln Arg Met Leu Asp Thr Glu Lys Gln Ser Arg Ala Arg	690	695	700
Ala Asp Gln Arg Ile Thr Glu Ser Arg Gln Val Val Glu Leu Ala Val	705	710	715
			720

Lys Glu His Lys Ala Glu Ile Leu Ala Leu Gln Gln Ala Leu Lys Glu  
 725 730 735  
 Gln Lys Leu Lys Ala Glu Ser Leu Ser Asp Lys Leu Asn Asp Leu Glu  
 740 745 750  
 Lys Lys His Ala Met Leu Glu Met Asn Ala Arg Ser Leu Gln Gln Lys  
 755 760 765  
 Leu Glu Thr Glu Arg Glu Leu Lys Gln Arg Leu Leu Glu Glu Gln Ala  
 770 775 780  
 Lys Leu Gln Gln Gln Met Asp Leu Gln Lys Asn His Ile Phe Arg Leu  
 785 790 795 800  
 Thr Gln Gly Leu Gln Glu Ala Leu Asp Arg Ala Asp Leu Leu Lys Thr  
 805 810 815  
 Glu Arg Ser Asp Leu Glu Tyr Gln Leu Glu Asn Ile Gln Val Leu Tyr  
 820 825 830  
 Ser His Glu Lys Val Lys Met Glu Gly Thr Ile Ser Gln Gln Thr Lys  
 835 840 845  
 Leu Ile Asp Phe Leu Gln Ala Lys Met Asp Gln Pro Ala Lys Lys Lys  
 850 855 860  
 Lys Val Pro Leu Gln Tyr Asn Glu Leu Lys Leu Ala Leu Glu Lys Glu  
 865 870 875 880  
 Lys Ala Arg Cys Ala Glu Leu Glu Glu Ala Leu Gln Lys Thr Arg Ile  
 885 890 895  
 Glu Leu Arg Ser Ala Arg Glu Glu Ala Ala His Arg Lys Ala Thr Asp  
 900 905 910  
 His Pro His Pro Ser Thr Pro Ala Thr Ala Arg Gln Gln Ile Ala Met  
 915 920 925  
 Ser Ala Ile Val Arg Ser Pro Glu His Gln Pro Ser Ala Met Ser Leu  
 930 935 940  
 Leu Ala Pro Pro Ser Ser Arg Arg Lys Glu Ser Ser Thr Pro Glu Glu  
 945 950 955 960  
 Phe Ser Arg Arg Leu Lys Glu Arg Met His His Asn Ile Pro His Arg  
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 Phe Asn Val Gly Leu Asn Met Arg Ala Thr Lys Cys Ala Val Cys Leu  
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 Asp Thr Val His Phe Gly Arg Gln Ala Ser Lys Cys Leu Glu Cys Gln  
 995 1000 1005  
 Val Met Cys His Pro Lys Cys Ser Thr Cys Leu Pro Ala Thr Cys Gly  
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 Leu Pro Ala Glu Tyr Ala Thr His Phe Thr Glu Ala Phe Cys Arg Asp  
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 Lys Met Asn Ser Pro Gly Leu Gln Ser Lys Glu Pro Gly Ser Ser Leu  
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His Leu Glu Gly Trp Met Lys Val Pro Arg Asn Asn Lys Arg Gly Gln  
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 Gln Gly Trp Asp Arg Lys Tyr Ile Val Leu Glu Gly Ser Lys Val Leu  
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 1090 1095 1100  
 Phe Glu Leu Cys Leu Pro Asp Gly Asp Val Ser Ile His Gly Ala Val  
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 Gly Ala Ser Glu Leu Ala Asn Thr Ala Lys Ala Asp Val Pro Tyr Ile  
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 Leu Lys Met Glu Ser His Pro His Thr Thr Cys Trp Pro Gly Arg Thr  
 1140 1145 1150  
 Leu Tyr Leu Leu Ala Pro Ser Phe Pro Asp Lys Gln Arg Trp Val Thr  
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 1170 1175 1180  
 Glu Ala Asp Ala Lys Leu Leu Gly Asn Ser Leu Leu Lys Leu Glu Gly  
 1185 1190 1195 1200  
 Asp Asp Arg Leu Asp Met Asn Cys Thr Leu Pro Phe Ser Asp Gln Val  
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 Asn Ser Leu Thr His Ile Pro Gly Ile Gly Ala Val Phe Gln Ile Tyr  
 1235 1240 1245  
 Ile Ile Lys Asp Leu Glu Lys Leu Leu Met Ile Ala Gly Glu Glu Arg  
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 Ala Leu Cys Leu Val Asp Val Lys Lys Val Lys Gln Ser Leu Ala Gln  
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 Ser His Leu Pro Ala Gln Pro Asp Val Ser Pro Asn Ile Phe Glu Ala  
 1285 1290 1295  
 Val Lys Gly Cys His Leu Phe Ala Ala Gly Lys Ile Glu Asn Ser Leu  
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 Cys Ile Cys Ala Ala Met Pro Ser Lys Val Val Ile Leu Arg Tyr Asn  
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 Asp Asn Leu Ser Lys Tyr Cys Ile Arg Lys Glu Ile Glu Thr Ser Glu  
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 Pro Cys Ser Cys Ile His Phe Thr Asn Tyr Ser Ile Leu Ile Gly Thr  
 1345 1350 1355 1360  
 Asn Lys Phe Tyr Glu Ile Asp Met Lys Gln Tyr Thr Leu Asp Glu Phe  
 1365 1370 1375  
 Leu Asp Lys Asn Asp His Ser Leu Ala Pro Ala Val Phe Ala Ser Ser

1380	1385	1390
Ser Asn Ser Phe Pro Val Ser Ile Val Gln Ala Asn Ser Ala Gly Gln 1395 1400 1405		
Arg Glu Glu Tyr Leu Leu Cys Phe His Glu Phe Gly Val Phe Val Asp 1410 1415 1420		
Ser Tyr Gly Arg Arg Ser Arg Thr Asp Asp Leu Lys Trp Ser Arg Leu 1425 1430 1435 1440		
Pro Leu Ala Phe Ala Tyr Arg Glu Pro Tyr Leu Phe Val Thr His Phe 1445 1450 1455		
Asn Ser Leu Glu Val Ile Glu Ile Gln Ala Arg Ser Ser Leu Gly Ser 1460 1465 1470		
Pro Ala Arg Ala Tyr Leu Glu Ile Pro Asn Pro Arg Tyr Leu Gly Pro 1475 1480 1485		
Ala Ile Ser Ser Gly Ala Ile Tyr Leu Ala Ser Ser Tyr Gln Asp Lys 1490 1495 1500		
Leu Arg Val Ile Cys Cys Lys Gly Asn Leu Val Lys Glu Ser Gly Thr 1505 1510 1515 1520		
Glu Gln His Arg Val Pro Ser Thr Ser Arg Ser Ser Pro Asn Lys Arg 1525 1530 1535		
Gly Pro Pro Thr Tyr Asn Glu His Ile Thr Lys Arg Val Ala Ser Ser 1540 1545 1550		
Pro Ala Pro Pro Glu Gly Pro Ser His Pro Arg Glu Pro Ser Thr Pro 1555 1560 1565		
His Arg Tyr Arg Asp Arg Glu Gly Arg Thr Glu Leu Arg Arg Asp Lys 1570 1575 1580		
Ser Pro Gly Arg Pro Leu Glu Arg Glu Lys Ser Pro Gly Arg Met Leu 1585 1590 1595 1600		
Ser Thr Arg Arg Glu Arg Ser Pro Gly Arg Leu Phe Glu Asp Ser Ser 1605 1610 1615		
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Asn Lys Val Trp Asp Gln Ser Ser Val 1635 1640		

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 <212> PRT  
 <213> Mus musculus

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 Ala Thr Tyr Ile Thr Glu Cys Ser Ser Leu Lys Arg Ser Leu Glu Gln  
 50 55 60  
 Ala Arg Met Glu Val Ser Gln Glu Asp Asp Lys Ala Leu Gln Leu Leu  
 65 70 75 80  
 His Asp Ile Arg Glu Gln Ser Arg Lys Leu Gln Glu Ile Lys Glu Gln  
 85 90 95  
 Glu Tyr Gln Ala Gln Val Glu Glu Met Arg Leu Met Met Asn Gln Leu  
 100 105 110  
 Glu Glu Asp Leu Val Ser Ala Arg Arg Arg Ser Asp Leu Tyr Glu Ser  
 115 120 125  
 Glu Leu Arg Glu Ser Arg Leu Ala Ala Glu Glu Phe Lys Arg Lys Ala  
 130 135 140  
 Asn Glu Cys Gln His Lys Leu Met Lys Ala Lys Asp Gln Gly Lys Pro  
 145 150 155 160  
 Glu Val Gly Glu Tyr Ser Lys Leu Glu Lys Ile Asn Ala Glu Gln Gln  
 165 170 175  
 Leu Lys Ile Gln Glu Leu Gln Glu Lys Leu Glu Lys Ala Val Lys Ala  
 180 185 190  
 Ser Thr Glu Ala Thr Glu Leu Leu Gln Asn Ile Arg Gln Ala Lys Glu  
 195 200 205  
 Arg Ala Glu Arg Glu Leu Glu Lys Leu His Asn Arg Glu Asp Ser Ser  
 210 215 220  
 Glu Gly Ile Lys Lys Lys Leu Val Glu Ala Glu Glu Arg Arg His Ser  
 225 230 235 240  
 Leu Glu Asn Lys Val Lys Arg Leu Glu Thr Met Glu Arg Arg Glu Asn  
 245 250 255  
 Arg Leu Lys Asp Asp Ile Gln Thr Lys Ser Glu Gln Ile Gln Gln Met  
 260 265 270  
 Ala Asp Lys Ile Leu Glu Leu Glu Glu Lys His Arg Glu Ala Gln Val  
 275 280 285  
 Ser Ala Gln His Leu Glu Val His Leu Lys Gln Lys Glu Gln His Tyr  
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 Glu Glu Lys Ile Lys Val Leu Asp Asn Gln Ile Lys Lys Asp Leu Ala  
 305 310 315 320  
 Asp Lys Glu Ser Leu Glu Asn Met Met Gln Arg His Glu Glu Glu Ala  
 325 330 335  
 His Glu Lys Gly Lys Ile Leu Ser Glu Gln Lys Ala Met Ile Asn Ala  
 340 345 350  
 Met Asp Ser Lys Ile Arg Ser Leu Glu Gln Arg Ile Val Glu Leu Ser

355	360	365
Glu Ala Asn Lys Leu Ala Ala Asn Ser Ser Leu Phe Thr Gln Arg Asn 370 375 380		
Met Lys Ala Gln Glu Glu Met Ile Ser Glu Leu Arg Gln Gln Lys Phe 385 390 395 400		
Tyr Leu Glu Thr Gln Ala Gly Lys Leu Glu Ala Gln Asn Arg Lys Leu 405 410 415		
Glu Glu Gln Leu Glu Lys Ile Ser His Gln Asp His Ser Asp Lys Ser 420 425 430		
Arg Leu Leu Glu Leu Glu Thr Arg Leu Arg Glu Val Ser Leu Glu His 435 440 445		
Glu Glu Gln Lys Leu Glu Leu Lys Arg Gln Leu Thr Glu Leu Gln Leu 450 455 460		
Ser Leu Gln Glu Arg Glu Ser Gln Leu Thr Ala Leu Gln Ala Ala Arg 465 470 475 480		
Ala Ala Leu Glu Ser Gln Leu Arg Gln Ala Lys Thr Glu Leu Glu Glu 485 490 495		
Thr Thr Ala Glu Ala Glu Glu Glu Ile Gln Ala Leu Thr Ala His Arg 500 505 510		
Asp Glu Ile Gln Arg Lys Phe Asp Ala Leu Arg Asn Ser Cys Thr Val 515 520 525		
Ile Thr Asp Leu Glu Glu Gln Leu Asn Gln Leu Thr Glu Asp Asn Ala 530 535 540		
Glu Leu Asn Asn Gln Asn Phe Tyr Leu Ser Lys Gln Leu Asp Glu Ala 545 550 555 560		
Ser Gly Ala Asn Asp Glu Ile Val Gln Leu Arg Ser Glu Val Asp His 565 570 575		
Leu Arg Arg Glu Ile Thr Glu Arg Glu Met Gln Leu Thr Ser Gln Lys 580 585 590		
Gln Thr Met Glu Ala Leu Lys Thr Thr Cys Thr Met Leu Glu Glu Gln 595 600 605		
Val Leu Asp Leu Glu Ala Leu Asn Asp Glu Leu Leu Glu Lys Glu Arg 610 615 620		
Gln Trp Glu Ala Trp Arg Ser Val Leu Gly Asp Glu Lys Ser Gln Phe 625 630 635 640		
Glu Cys Arg Val Arg Glu Leu Gln Arg Met Leu Asp Thr Glu Lys Gln 645 650 655		
Ser Arg Ala Arg Ala Asp Gln Arg Ile Thr Glu Ser Arg Gln Val Val 660 665 670		
Glu Leu Ala Val Lys Glu His Lys Ala Glu Ile Leu Ala Leu Gln Gln 675 680 685		

Ala Leu Lys Glu Gln Lys Leu Lys Ala Glu Ser Leu Ser Asp Lys Leu  
 690 695 700  
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 Glu Glu Gln Ala Lys Leu Gln Gln Gln Met Asp Leu Gln Lys Asn His  
 740 745 750  
 Ile Phe Arg Leu Thr Gln Gly Leu Gln Glu Ala Leu Asp Arg Ala Asp  
 755 760 765  
 Leu Leu Lys Thr Glu Arg Ser Asp Leu Glu Tyr Gln Leu Glu Asn Ile  
 770 775 780  
 Gln Val Leu Tyr Ser His Glu Lys Val Lys Met Glu Gly Thr Ile Ser  
 785 790 795 800  
 Gln Gln Thr Lys Leu Ile Asp Phe Leu Gln Ala Lys Met Asp Gln Pro  
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 850 855 860  
 Lys Ala Thr Asp His Pro His Pro Ser Thr Pro Ala Thr Ala Arg Gln  
 865 870 875 880  
 Gln Ile Ala Met Ser Ala Ile Val Arg Ser Pro Glu His Gln Pro Ser  
 885 890 895  
 Ala Met Ser Leu Leu Ala Pro Pro Ser Ser Arg Arg Lys Glu Ser Ser  
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 Thr Pro Glu Glu Phe Ser Arg Arg Leu Lys Glu Arg Met His His Asn  
 915 920 925  
 Ile Pro His Arg Phe Asn Val Gly Leu Asn Met Arg Ala Thr Lys Cys  
 930 935 940  
 Ala Val Cys Leu Asp Thr Val His Phe Gly Arg Gln Ala Ser Lys Cys  
 945 950 955 960  
 Leu Glu Cys Gln Val Met Cys His Pro Lys Cys Ser Thr Cys Leu Pro  
 965 970 975  
 Ala Thr Cys Gly Leu Pro Ala Glu Tyr Ala Thr His Phe Thr Glu Ala  
 980 985 990  
 Phe Cys Arg Asp Lys Met Asn Ser Pro Gly Leu Gln Ser Lys Glu Pro  
 995 1000 1005  
 Gly Ser Ser Leu His Leu Glu Gly Trp Met Lys Val Pro Arg Asn Asn  
 1010 1015 1020

Lys Arg Gly Gln Gln Gly Trp Asp Arg Lys Tyr Ile Val Leu Glu Gly  
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 Ser Lys Val Leu Ile Tyr Asp Asn Glu Ala Arg Glu Ala Gly Gln Arg  
 1045 1050 1055  
 Pro Val Glu Glu Phe Glu Leu Cys Leu Pro Asp Gly Asp Val Ser Ile  
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 His Gly Ala Val Gly Ala Ser Glu Leu Ala Asn Thr Ala Lys Ala Asp  
 1075 1080 1085  
 Val Pro Tyr Ile Leu Lys Met Glu Ser His Pro His Thr Thr Cys Trp  
 1090 1095 1100  
 Pro Gly Arg Thr Leu Tyr Leu Leu Ala Pro Ser Phe Pro Asp Lys Gln  
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 1140 1145 1150  
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 1155 1160 1165  
 Ser Asp Gln Val Val Leu Val Gly Thr Glu Glu Gly Leu Tyr Ala Leu  
 1170 1175 1180  
 Asn Val Leu Lys Asn Ser Leu Thr His Ile Pro Gly Ile Gly Ala Val  
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 Phe Gln Ile Tyr Ile Ile Lys Asp Leu Glu Lys Leu Leu Met Ile Ala  
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 Gly Glu Glu Arg Ala Leu Cys Leu Val Asp Val Lys Lys Val Lys Gln  
 1220 1225 1230  
 Ser Leu Ala Gln Ser His Leu Pro Ala Gln Pro Asp Val Ser Pro Asn  
 1235 1240 1245  
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 1250 1255 1260  
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 1265 1270 1275 1280  
 Leu Arg Tyr Asn Asp Asn Leu Ser Lys Tyr Cys Ile Arg Lys Glu Ile  
 1285 1290 1295  
 Glu Thr Ser Glu Pro Cys Ser Cys Ile His Phe Thr Asn Tyr Ser Ile  
 1300 1305 1310  
 Leu Ile Gly Thr Asn Lys Phe Tyr Glu Ile Asp Met Lys Gln Tyr Thr  
 1315 1320 1325  
 Leu Asp Glu Phe Leu Asp Lys Asn Asp His Ser Leu Ala Pro Ala Val  
 1330 1335 1340  
 Phe Ala Ser Ser Ser Asn Ser Phe Pro Val Ser Ile Val Gln Ala Asn

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 Ser Ala Gly Gln Arg Glu Glu Tyr Leu Leu Cys Phe His Glu Phe Gly  
                                  1365                      1370                      1375  
 Val Phe Val Asp Ser Tyr Gly Arg Arg Ser Arg Thr Asp Asp Leu Lys  
                                  1380                      1385                      1390  
 Trp Ser Arg Leu Pro Leu Ala Phe Ala Tyr Arg Glu Pro Tyr Leu Phe  
                                  1395                      1400                      1405  
 Val Thr His Phe Asn Ser Leu Glu Val Ile Glu Ile Gln Ala Arg Ser  
                                  1410                      1415                      1420  
 Ser Leu Gly Ser Pro Ala Arg Ala Tyr Leu Glu Ile Pro Asn Pro Arg  
 1425                      1430                      1435                      1440  
 Tyr Leu Gly Pro Ala Ile Ser Ser Gly Ala Ile Tyr Leu Ala Ser Ser  
                                  1445                      1450                      1455  
 Tyr Gln Asp Lys Leu Arg Val Ile Cys Cys Lys Gly Asn Leu Val Lys  
                                  1460                      1465                      1470  
 Glu Ser Gly Thr Glu Gln His Arg Val Pro Ser Thr Ser Arg Ser Ser  
                                  1475                      1480                      1485  
 Pro Asn Lys Arg Gly Pro Pro Thr Tyr Asn Glu His Ile Thr Lys Arg  
                                  1490                      1495                      1500  
 Val Ala Ser Ser Pro Ala Pro Pro Glu Gly Pro Ser His Pro Arg Glu  
 1505                      1510                      1515                      1520  
 Pro Ser Thr Pro His Arg Tyr Arg Asp Arg Glu Gly Arg Thr Glu Leu  
                                  1525                      1530                      1535  
 Arg Arg Asp Lys Ser Pro Gly Arg Pro Leu Glu Arg Glu Lys Ser Pro  
                                  1540                      1545                      1550  
 Gly Arg Met Leu Ser Thr Arg Arg Glu Arg Ser Pro Gly Arg Leu Phe  
                                  1555                      1560                      1565  
 Glu Asp Ser Ser Arg Gly Arg Leu Pro Ala Gly Ala Val Arg Thr Pro  
                                  1570                      1575                      1580  
 Leu Ser Gln Val Asn Lys Val Trp Asp Gln Ser Ser Val  
 1585                      1590                      1595

<210> 7  
 <211> 1286  
 <212> PRT  
 <213> Homo sapiens

<400> 7  
 Val Leu Asp Asn Gln Ile Lys Lys Asp Leu Ala Asp Lys Glu Thr Leu  
   1                                  5                                  10                                  15  
 Glu Asn Met Met Gln Arg His Glu Glu Glu Ala His Glu Lys Gly Lys  
                                   20                                  25                                  30  
 Ile Leu Ser Glu Gln Lys Ala Met Ile Asn Ala Met Asp Ser Lys Ile  
                                   35                                  40                                  45

Arg Ser Leu Glu Gln Arg Ile Val Glu Leu Ser Glu Ala Asn Lys Leu  
 50 55 60  
 Ala Ala Asn Ser Ser Leu Phe Thr Gln Arg Asn Met Lys Ala Gln Glu  
 65 70 75 80  
 Glu Met Ile Ser Glu Leu Arg Gln Gln Lys Phe Tyr Leu Glu Thr Gln  
 85 90 95  
 Ala Gly Lys Leu Glu Ala Gln Asn Arg Lys Leu Glu Glu Gln Leu Glu  
 100 105 110  
 Lys Ile Ser His Gln Asp His Ser Asp Lys Asn Arg Leu Leu Glu Leu  
 115 120 125  
 Glu Thr Arg Leu Arg Glu Val Ser Leu Glu His Glu Glu Gln Lys Leu  
 130 135 140  
 Glu Leu Lys Arg Gln Leu Thr Glu Leu Gln Leu Ser Leu Gln Glu Arg  
 145 150 155 160  
 Glu Ser Gln Leu Thr Ala Leu Gln Ala Ala Arg Ala Ala Leu Glu Ser  
 165 170 175  
 Gln Leu Arg Gln Ala Lys Thr Glu Leu Glu Glu Thr Thr Ala Glu Ala  
 180 185 190  
 Glu Glu Glu Ile Gln Ala Leu Thr Ala His Arg Asp Glu Ile Gln Arg  
 195 200 205  
 Lys Phe Asp Ala Leu Arg Asn Ser Cys Thr Val Ile Thr Asp Leu Glu  
 210 215 220  
 Glu Gln Leu Asn Gln Leu Thr Glu Asp Asn Ala Glu Leu Asn Asn Gln  
 225 230 235 240  
 Asn Phe Tyr Leu Ser Lys Gln Leu Asp Glu Ala Ser Gly Ala Asn Asp  
 245 250 255  
 Glu Ile Val Gln Leu Arg Ser Glu Val Asp His Leu Arg Arg Glu Ile  
 260 265 270  
 Thr Glu Arg Glu Met Gln Leu Thr Ser Gln Lys Gln Thr Met Glu Ala  
 275 280 285  
 Leu Lys Thr Thr Cys Thr Met Leu Glu Glu Gln Val Met Asp Leu Glu  
 290 295 300  
 Ala Leu Asn Asp Glu Leu Leu Glu Lys Glu Arg Gln Trp Glu Ala Trp  
 305 310 315 320  
 Arg Ser Val Leu Gly Asp Glu Lys Ser Gln Phe Glu Cys Arg Val Arg  
 325 330 335  
 Glu Leu Gln Arg Met Leu Asp Thr Glu Lys Gln Ser Arg Ala Arg Ala  
 340 345 350  
 Asp Gln Arg Ile Thr Glu Ser Arg Gln Val Val Glu Leu Ala Val Lys  
 355 360 365  
 Glu His Lys Ala Glu Ile Leu Ala Leu Gln Gln Ala Leu Lys Glu Gln

370	375	380
Lys Leu Lys Ala Glu Ser Leu Ser Asp Lys Leu Asn Asp Leu Glu Lys		
385	390	395 400
Lys His Ala Met Leu Glu Met Asn Ala Arg Ser Leu Gln Gln Lys Leu		
	405	410 415
Glu Thr Glu Arg Glu Leu Lys Gln Arg Leu Leu Glu Glu Gln Ala Lys		
	420	425 430
Leu Gln Gln Gln Met Asp Leu Gln Lys Asn His Ile Phe Arg Leu Thr		
	435	440 445
Gln Gly Leu Gln Glu Ala Leu Asp Arg Ala Asp Leu Leu Lys Thr Glu		
	450	455 460
Arg Ser Asp Leu Glu Tyr Gln Leu Glu Asn Ile Gln Val Leu Tyr Ser		
	465	470 475 480
His Glu Lys Val Lys Met Glu Gly Thr Ile Ser Gln Gln Thr Lys Leu		
	485	490 495
Ile Asp Phe Leu Gln Ala Lys Met Asp Gln Pro Ala Lys Lys Lys Lys		
	500	505 510
Val Pro Leu Gln Tyr Asn Glu Leu Lys Leu Ala Leu Glu Lys Glu Lys		
	515	520 525
Ala Arg Cys Ala Glu Leu Glu Glu Ala Leu Gln Lys Thr Arg Ile Glu		
	530	535 540
Leu Arg Ser Ala Arg Glu Glu Ala Ala His Arg Lys Ala Thr Asp His		
	545	550 555 560
Pro His Pro Ser Thr Pro Ala Thr Ala Arg Gln Gln Ile Ala Met Ser		
	565	570 575
Ala Ile Val Arg Ser Pro Glu His Gln Pro Ser Ala Met Ser Leu Leu		
	580	585 590
Ala Pro Pro Ser Ser Arg Arg Lys Glu Ser Ser Thr Pro Glu Glu Phe		
	595	600 605
Ser Arg Arg Leu Lys Glu Arg Met His His Asn Ile Pro His Arg Phe		
	610	615 620
Asn Val Gly Leu Asn Met Arg Ala Thr Lys Cys Ala Val Cys Leu Asp		
	625	630 635 640
Thr Val His Phe Gly Arg Gln Ala Ser Lys Cys Leu Glu Cys Gln Val		
	645	650 655
Met Cys His Pro Lys Cys Ser Thr Cys Leu Pro Ala Thr Cys Gly Leu		
	660	665 670
Pro Ala Glu Tyr Ala Thr His Phe Thr Glu Ala Phe Cys Arg Asp Lys		
	675	680 685
Met Asn Ser Pro Gly Leu Gln Thr Lys Glu Pro Ser Ser Ser Leu His		
	690	695 700

Leu Glu Gly Trp Met Lys Val Pro Arg Asn Asn Lys Arg Gly Gln Gln  
 705 710 715 720  
 Gly Trp Asp Arg Lys Tyr Ile Val Leu Glu Gly Ser Lys Val Leu Ile  
 725 730 735  
 Tyr Asp Asn Glu Ala Arg Glu Ala Gly Gln Arg Pro Val Glu Glu Phe  
 740 745 750  
 Glu Leu Cys Leu Pro Asp Gly Asp Val Ser Ile His Gly Ala Val Gly  
 755 760 765  
 Ala Ser Glu Leu Ala Asn Thr Ala Lys Ala Asp Val Pro Tyr Ile Leu  
 770 775 780  
 Lys Met Glu Ser His Pro His Thr Thr Cys Trp Pro Gly Arg Thr Leu  
 785 790 795 800  
 Tyr Leu Leu Ala Pro Ser Phe Pro Asp Lys Gln Arg Trp Val Thr Ala  
 805 810 815  
 Leu Glu Ser Val Val Ala Gly Gly Arg Val Ser Arg Glu Lys Ala Glu  
 820 825 830  
 Ala Asp Ala Lys Leu Leu Gly Asn Ser Leu Leu Lys Leu Glu Gly Asp  
 835 840 845  
 Asp Arg Leu Asp Met Asn Cys Thr Leu Pro Phe Ser Asp Gln Val Val  
 850 855 860  
 Leu Val Gly Thr Glu Glu Gly Leu Tyr Ala Leu Asn Val Leu Lys Asn  
 865 870 875 880  
 Ser Leu Thr His Val Pro Gly Ile Gly Ala Val Phe Gln Ile Tyr Ile  
 885 890 895  
 Ile Lys Asp Leu Glu Lys Leu Leu Met Ile Ala Gly Glu Glu Arg Ala  
 900 905 910  
 Leu Cys Leu Val Asp Val Lys Lys Val Lys Gln Ser Leu Ala Gln Ser  
 915 920 925  
 His Leu Pro Ala Gln Pro Asp Ile Ser Pro Asn Ile Phe Glu Ala Val  
 930 935 940  
 Lys Gly Cys His Leu Phe Gly Ala Gly Lys Ile Glu Asn Gly Leu Cys  
 945 950 955 960  
 Ile Cys Ala Ala Met Pro Ser Lys Val Val Ile Leu Arg Tyr Asn Glu  
 965 970 975  
 Asn Leu Ser Lys Tyr Cys Ile Arg Lys Glu Ile Glu Thr Ser Glu Pro  
 980 985 990  
 Cys Ser Cys Ile His Phe Thr Asn Tyr Ser Ile Leu Ile Gly Thr Asn  
 995 1000 1005  
 Lys Phe Tyr Glu Ile Asp Met Lys Gln Tyr Thr Leu Glu Glu Phe Leu  
 1010 1015 1020  
 Asp Lys Asn Asp His Ser Leu Ala Pro Ala Val Phe Ala Ala Ser Ser  
 1025 1030 1035 1040

Asn Ser Phe Pro Val Ser Ile Val Gln Val Asn Ser Ala Gly Gln Arg  
 1045 1050 1055  
 Glu Glu Tyr Leu Leu Cys Phe His Glu Phe Gly Val Phe Val Asp Ser  
 1060 1065 1070  
 Tyr Gly Arg Arg Ser Arg Thr Asp Asp Leu Lys Trp Ser Arg Leu Pro  
 1075 1080 1085  
 Leu Ala Phe Ala Tyr Arg Glu Pro Tyr Leu Phe Val Thr His Phe Asn  
 1090 1095 1100  
 Ser Leu Glu Val Ile Glu Ile Gln Ala Arg Ser Ser Ala Gly Thr Pro  
 1105 1110 1115 1120  
 Ala Arg Ala Tyr Leu Asp Ile Pro Asn Pro Arg Tyr Leu Gly Pro Ala  
 1125 1130 1135  
 Ile Ser Ser Gly Ala Ile Tyr Leu Ala Ser Ser Tyr Gln Asp Lys Leu  
 1140 1145 1150  
 Arg Val Ile Cys Cys Lys Gly Asn Leu Val Lys Glu Ser Gly Thr Glu  
 1155 1160 1165  
 His His Arg Gly Pro Ser Thr Ser Arg Ser Ser Pro Asn Lys Arg Gly  
 1170 1175 1180  
 Pro Pro Thr Tyr Asn Glu His Ile Thr Lys Arg Val Ala Ser Ser Pro  
 1185 1190 1195 1200  
 Ala Pro Pro Glu Gly Pro Ser His Pro Arg Glu Pro Ser Thr Pro His  
 1205 1210 1215  
 Arg Tyr Arg Glu Gly Arg Thr Glu Leu Arg Arg Asp Lys Ser Pro Gly  
 1220 1225 1230  
 Arg Pro Leu Glu Arg Glu Lys Ser Pro Gly Arg Met Leu Ser Thr Arg  
 1235 1240 1245  
 Arg Glu Arg Ser Pro Gly Arg Leu Phe Glu Asp Ser Ser Arg Gly Arg  
 1250 1255 1260  
 Leu Pro Ala Gly Ala Val Arg Thr Pro Leu Ser Gln Val Asn Lys Val  
 1265 1270 1275 1280  
 Trp Asp Gln Ser Ser Val  
 1285